

WO03059884

Publication Title:

MODULATORS OF LXR

Abstract:

Compounds, compositions and methods for modulating the activity of nuclear receptors are provided. In particular, heterocyclic compounds are provided for modulating the activity of nuclear receptors, including liver X receptor (LXR) and orphan nuclear receptors. In certain embodiments, the compounds are N-substituted pyridones.

Data supplied from the esp@cenet database - <http://ep.espacenet.com>

(19) World Intellectual Property Organization
International Bureau



(43) International Publication Date
24 July 2003 (24.07.2003)

PCT

(10) International Publication Number
WO 03/059884 A1

(51) International Patent Classification⁷: **C07D 213/64**,
A61K 31/4412, 31/4418

(21) International Application Number: PCT/US02/41306

(22) International Filing Date:
20 December 2002 (20.12.2002)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
60/342,707 21 December 2001 (21.12.2001) US

(63) Related by continuation (CON) or continuation-in-part
(CIP) to earlier application:
US 60/342,707 (CIP)
Filed on 21 December 2001 (21.12.2001)

(71) Applicant (for all designated States except US): **X-CEPTOR THERAPEUTICS, INC.** [US/US]; 4757 Nexus
Centre Drive, Suite 200, San Diego, CA 92121 (US).

(72) Inventors; and

(75) Inventors/Applicants (for US only): **BAYNE, Christopher, D.** [US/US]; 3149 Clairemont Drive, Apt. 4, San
Diego, CA 92117 (US). **JOHNSON, Alan, T.** [US/US];
17058 Iron Mountain Drive, Poway, CA 92064 (US). **LU, Shao-Po** [CN/US]; 11693 Ramsdell Court, San Diego, CA
92131 (US). **MOHAN, Raju** [US/US]; 3125 Caminito Ri-
cardo, Encinitas, CA 92024 (US). **GRIFFITH, Ronald, C.**
[US/US]; 2508 Russett Glen, Escondido, CA 92029 (US).

(74) Agents: **SEIDMAN, Stephanie, L.** et al.; Heller Ehrman
White & McAuliffe LLP, 4350 La Jolla Village Drive, 7th
Floor, San Diego, CA 92122-1246 (US).

(81) Designated States (national): AE, AG, AL, AM, AT, AU,
AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU,

CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH,
GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC,
LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW,
MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD, SE,
SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ,
VC, VN, YU, ZA, ZM, ZW.

(84) Designated States (regional): ARIPO patent (GH, GM,
KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW),
Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM),
European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE,
ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, SI, SK,
TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ,
GW, ML, MR, NE, SN, TD, TG).

Declaration under Rule 4.17:

— as to the applicant's entitlement to claim the priority of the
earlier application (Rule 4.17(iii)) for the following desig-
nations AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY,
BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC,
EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS,
JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA,
MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL,
PT, RO, RU, SC, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT,
TZ, UA, UG, UZ, VC, VN, YU, ZA, ZM, ZW, ARIPO patent
(GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW),
Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM),
European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE,
ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, SI, SK,
TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ,
GW, ML, MR, NE, SN, TD, TG)

Published:

— with international search report
— before the expiration of the time limit for amending the
claims and to be republished in the event of receipt of
amendments

For two-letter codes and other abbreviations, refer to the "Guid-
ance Notes on Codes and Abbreviations" appearing at the begin-
ning of each regular issue of the PCT Gazette.

(54) Title: MODULATORS OF LXR

(57) Abstract: Compounds, compositions and methods for modulating the activity of nuclear receptors are provided. In particular, heterocyclic compounds are provided for modulating the activity of nuclear receptors, including liver X receptor (LXR) and orphan nuclear receptors. In certain embodiments, the compounds are N-substituted pyridones.



WO 03/059884 A1

MODULATORS OF LXR

RELATED APPLICATIONS

Benefit of priority is claimed herein to U.S. provisional patent
5 application No. 60/342,707, filed December 21, 2001, to Bayne *et al.*,
entitled "MODULATORS OF LXR". For U.S. national stage purposes and
where appropriate, the disclosure of the above-referenced application is
incorporated by reference herein in its entirety.

FIELD OF THE INVENTION

Compounds, compositions and methods for modulating the activity
of liver X receptors (LXRs) are provided. In particular, pyridone
derivatives are provided for modulating the activity of LXRs.

5 BACKGROUND OF THE INVENTION

Nuclear Receptors

Nuclear receptors are a superfamily of regulatory proteins that are
structurally and functionally related and are receptors for, *e.g.*, steroids,
retinoids, vitamin D and thyroid hormones (see, *e.g.*, Evans (1988)
10 *Science* 240:889-895). These proteins bind to cis-acting elements in the
promoters of their target genes and modulate gene expression in
response to ligands for the receptors.

Nuclear receptors can be classified based on their DNA binding
properties (see, *e.g.*, Evans, *supra* and Glass (1994) *Endocr. Rev.*
15 15:391-407). For example, one class of nuclear receptors includes the
glucocorticoid, estrogen, androgen, progestin and mineralocorticoid
receptors which bind as homodimers to hormone response elements
(HREs) organized as inverted repeats (see, *e.g.*, Glass, *supra*). A second
class of receptors, including those activated by retinoic acid, thyroid
20 hormone, vitamin D₃, fatty acids/peroxisome proliferators (*i.e.*,
peroxisome proliferator activated receptors or PPARs) and ecdysone, bind
to HREs as heterodimers with a common partner, the retinoid X receptors

-2-

(*i.e.*, RXRs, also known as the 9-*cis* retinoic acid receptors; see, *e.g.*, Levin *et al.* (1992) *Nature* 355:359-361 and Heyman *et al.* (1992) *Cell* 68:397-406).

RXRs are unique among the nuclear receptors in that they bind
5 DNA as a homodimer and are required as a heterodimeric partner for a number of additional nuclear receptors to bind DNA (see, *e.g.*, Mangelsdorf *et al.* (1995) *Cell* 83:841-850). The latter receptors, termed the class II nuclear receptor subfamily, include many which are established or implicated as important regulators of gene expression.
10 There are three RXR genes (see, *e.g.*, Mangelsdorf *et al.* (1992) *Genes Dev.* 6:329-344), coding for RXR α , - β , and - γ , all of which are able to heterodimerize with any of the class II receptors, although there appear to be preferences for distinct RXR subtypes by partner receptors *in vivo* (see, *e.g.*, Chiba *et al.* (1997) *Mol. Cell. Biol.* 17:3013-3020). In the
15 adult liver, RXR α is the most abundant of the three RXRs (see, *e.g.*, Mangelsdorf *et al.* (1992) *Genes Dev.* 6:329-344), suggesting that it might have a prominent role in hepatic functions that involve regulation by class II nuclear receptors. See also, Wan *et al.* (2000) *Mol. Cell. Biol.* 20:4436-4444.

20 Orphan Nuclear Receptors

Included in the nuclear receptor superfamily of regulatory proteins are nuclear receptors for whom the ligand is known and those which lack known ligands. Nuclear receptors falling in the latter category are referred to as orphan nuclear receptors. The search for activators for
25 orphan receptors has led to the discovery of previously unknown signaling pathways (see, *e.g.*, Levin *et al.*, (1992), *supra* and Heyman *et al.*, (1992), *supra*). For example, it has been reported that bile acids, which are involved in physiological processes such as cholesterol catabolism, are ligands for farnesoid X receptor (FXR).

Since it is known that products of intermediary metabolism act as transcriptional regulators in bacteria and yeast, such molecules may serve similar functions in higher organisms (see, *e.g.*, Tomkins (1975) *Science* 189:760-763 and O'Malley (1989) *Endocrinology* 125:1119-1120). For example, one biosynthetic pathway in higher eukaryotes is the mevalonate pathway, which leads to the synthesis of cholesterol, bile acids, porphyrin, dolichol, ubiquinone, carotenoids, retinoids, vitamin D, steroid hormones and farnesylated proteins.

LXR α and LXR β

10 LXR α is found predominantly in the liver, with lower levels found in kidney, intestine, spleen and adrenal tissue (see, *e.g.*, Willy, *et al.* (1995) *Gene Dev.* 9(9):1033-1045). LXR β is ubiquitous in mammals and was found in nearly all tissues examined. LXRs are activated by certain naturally occurring, oxidized derivatives of cholesterol (see, *e.g.*,
15 Lehmann, *et al.* (1997) *J. Biol. Chem.* 272(6):3137-3140). LXR α is activated by oxysterol and promotes cholesterol metabolism (Peet *et al.* (1998) *Cell* 93:693-704). Thus, LXRs appear to play a role in, *e.g.*, cholesterol metabolism (see, *e.g.*, Janowski, *et al.* (1996) *Nature* 383:728-731).

20 Nuclear Receptors and Disease

Nuclear receptor activity has been implicated in a variety of diseases and disorders, including, but not limited to, hypercholesterolemia (see, *e.g.*, International Patent Application Publication No. WO 00/57915), osteoporosis and vitamin deficiency (see,
25 *e.g.*, U.S. Patent No. 6,316,5103), hyperlipoproteinemia (see, *e.g.*, International Patent Application Publication No. WO 01/60818), hypertriglyceridemia, lipodystrophy, hyperglycemia and diabetes mellitus (see, *e.g.*, International Patent Application Publication No. WO 01/82917), atherosclerosis and gallstones (see, *e.g.*, International Patent

Application Publication No. WO 00/37077), disorders of the skin and mucous membranes (see, *e.g.*, U.S. Patent Nos. 6,184,215 and 6,187,814, and International Patent Application Publication No. WO 98/32444), acne (see, *e.g.*, International Patent Application Publication No. WO 00/49992), and cancer, Parkinson's disease and Alzheimer's disease (see, *e.g.*, International Patent Application Publication No. WO 00/17334). Activity of nuclear receptors, including LXRs, FXR and PPAR, and orphan nuclear receptors, has been implicated in physiological processes including, but not limited to, bile acid biosynthesis, cholesterol metabolism or catabolism, and modulation of cholesterol 7 α -hydroxylase gene (CYP7A1) transcription (see, *e.g.*, Chiang *et al.* (2000) *J. Biol. Chem.* 275:10918-10924), HDL metabolism (see, *e.g.*, Urizar *et al.* (2000) *J. Biol. Chem.* 275:39313-39317 and International Patent Application Publication No. WO 01/03705), and increased cholesterol efflux and increased expression of ATP binding cassette transporter protein (ABC1) (see, *e.g.*, International Patent Application Publication No. WO 00/78972).

Thus, there is a need for compounds, compositions and methods of modulating the activity of nuclear receptors, including LXRs, FXR, PPAR and orphan nuclear receptors. Such compounds are useful in the treatment, prevention, or amelioration of one or more symptoms of diseases or disorders in which nuclear receptor activity is implicated.

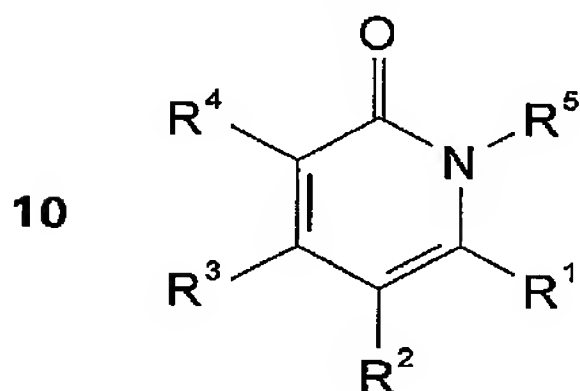
SUMMARY OF THE INVENTION

Compounds for use in compositions and methods for modulating the activity of nuclear receptors are provided. In particular, compounds for use in compositions and methods for modulating liver X receptors (LXR α and LXR β), FXR, PPAR and/or orphan nuclear receptors are provided. In certain embodiments, the compounds are N-substituted pyridone compounds. In one embodiment, the compounds provided

-5-

herein are agonists of LXR. In another embodiment, the compounds provided herein are antagonists of LXR. Agonists that exhibit low efficacy are, in certain embodiments, antagonists.

In one embodiment, the compounds for use in the compositions and methods provided herein have formula I:



where, R¹ is selected from substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted aralkyl, substituted or unsubstituted heteroaralkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted cycloalkenyl, substituted or unsubstituted cycloalkynyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted cycloalkylalkyl and substituted or unsubstituted heterocyclylalkyl;

R² is hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted aryl;

R³ and R⁴ are selected from (i), (ii), (iii) or (iv) as follows:

(i) R³ is substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted cycloalkenyl, substituted or unsubstituted cycloalkynyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted alkylaryl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, C(J)OR³⁰ or

-6-

$C(J)NR^{31}R^{32}$; and R^4 is hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, halide, pseudohalide, $C(J)R^{30}$, $C(J)OR^{30}$, $C(J)NR^{31}R^{32}$, $CH_2NR^{31}R^{32}$, CH_2OR^{31} , $CR^{30}=CR^{31}R^{32}$, NO_2 or $NR^{31}R^{32}$;

5 (ii) R^3 and R^4 , together with the atoms to which they are attached, form a substituted or unsubstituted heterocyclic ring;

(iii) R^3 and R^4 , together with the atoms to which they are attached, form a substituted or unsubstituted heterocyclic ring with the proviso that the nitrogen atom in the heterocyclic ring is not substituted with a
10 phenyl ring; or

(iv) R^3 and R^4 , together with the atoms to which they are attached, form a substituted or unsubstituted heterocyclic ring with the proviso that the heterocyclic ring does not have more than one oxo substituent;

R^5 is substituted or unsubstituted alkyl, substituted or
15 unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted aralkyl, substituted or unsubstituted aralkenyl, substituted or unsubstituted aralkynyl, substituted or unsubstituted heteroaralkyl, substituted or
20 unsubstituted heteroaralkenyl, substituted or unsubstituted heteroaralkynyl, $-N=CR^6R^7$ or $-NR^9R^{10}$;

R^6 and R^7 are each independently hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted cycloalkyl, substituted
25 or unsubstituted heterocyclyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted aralkyl, or substituted or unsubstituted heteroaralkyl; or together form substituted or unsubstituted alkylene, substituted or unsubstituted

-7-

alkenylene, substituted or unsubstituted alkynylene, or $-(CH_2)_xX(CH_2)_y-$ where x and y are each independently 1, 2 or 3, and X is O, S or NR^8 ;

R^8 is substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted alkylcarbonyl, substituted or unsubstituted arylcarbonyl, or substituted or unsubstituted heteroarylcarbonyl;

R^9 and R^{10} are each independently hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted aralkyl, or substituted or unsubstituted heteroaralkyl;

R^{30} is hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted cycloalkylalkyl, substituted or unsubstituted heterocyclalkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted aralkyl, or substituted or unsubstituted heteroaralkyl;

R^{31} and R^{32} are each independently hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted cycloalkylalkyl, substituted or unsubstituted heterocyclalkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted aralkyl, substituted or unsubstituted heteroaralkyl, $C(J)R^{35}$; or R^{31} and R^{32} , together with the atoms to which they are attached, form substituted or unsubstituted cycloalkyl ring, a substituted or unsubstituted heterocyclic ring or a substituted or unsubstituted heteroaryl ring;

-8-

J is O, S or NR⁴⁰;

R³⁵ is hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocyclyl,

5 substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted alkoxy, substituted or unsubstituted aralkoxy, substituted or unsubstituted alkylamino, substituted or unsubstituted dialkylamino, substituted or unsubstituted arylalkylamino, or substituted or unsubstituted diarylamino;

10 R⁴⁰ is hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl;

where the alkyl, alkenyl, alkynyl, cycloalkyl, heterocyclyl, alkylene, alkenylene, alkynylene, aryl, heteroaryl, aralkyl, aralkenyl, aralkynyl, heteroaralkyl, heteroaralkenyl and heteroaralkynyl moieties of R¹, R², R³,

15 R⁵, R⁶, R⁷, R⁸, R⁹ and R¹⁰ are unsubstituted or substituted with one or more substituents, in one embodiment, one to three or four substituents, each independently selected from Q¹, where Q¹ is halo, pseudohalo, hydroxy, oxo, thia, nitrile, nitro, formyl, mercapto, amino, hydroxyalkyl, hydroxyalkylaryloxy, hydroxyaryl, hydroxyalkylaryl, hydroxycarbonyl, hydroxycarbonylalkyl, alkyl, haloalkyl, polyhaloalkyl, aminoalkyl, diaminoalkyl, alkenyl containing 1 to 2 double bonds, alkynyl containing 1 to 2 triple bonds, cycloalkyl, cycloalkylalkyl, heterocyclyl, heterocyclylalkyl, aryl, diaryl, hydroxyaryl, alkylaryl, heteroaryl, aralkyl, aralkenyl, aralkynyl, alkylaralkyl, heteroarylalkyl, trialkylsilyl, dialkylarylsilyl, alkyl diarylsilyl, triarylsilyl, alkylidene, arylalkylidene, alkylcarbonyl, alkylarylcarbonyl, arylcarbonyl, heterocyclylcarbonyl, heteroarylcarbonyl, alkoxycarbonyl, alkoxycarbonylalkyl, alkoxycarbonylaryloxy, aryloxycarbonyl, aryloxycarbonylalkyl, heterocyclylcarbonylalkylaryl, aralkoxycarbonyl, aralkoxycarbonylalkyl,

20

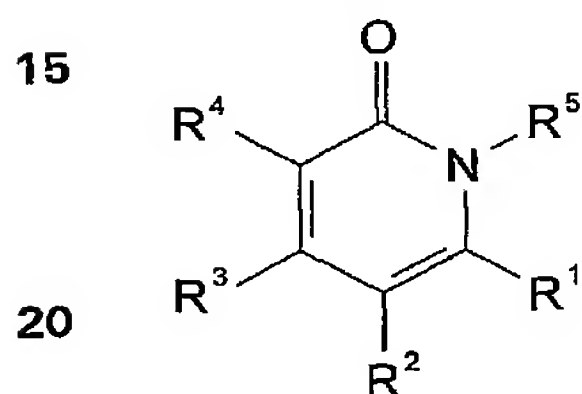
25

- arylcarbonylalkyl, aminocarbonyl, alkylaminocarbonyl,
 dialkylaminocarbonyl, arylaminocarbonyl, diarylaminocarbonyl,
 arylalkylaminocarbonyl, alkoxy, aryloxy, haloalkoxy, alkoxyaryloxy,
 alkylaryloxy, diaryloxy, alkylaryloxyalkyl, alkyl diaryloxy, perfluoroalkoxy,
 5 alkenyloxy, alkynyloxy, aryloxyalkoxy, aralkoxyaryloxy,
 alkylarylcyloalkoxy, heterocycloxy, alkoxyalkyl, alkoxyalkoxyalkyl,
 alkylheteroaryloxy, alkylcyloalkoxy, cycloalkoxy, heterocycloxy,
 aralkoxy, haloaryloxy, heteroaryloxy, alkylheteroaryloxy,
 alkoxycarbonylheterocycloxy, alkylcarbonylaryloxy, alkylcarbonyloxy,
 10 arylcarbonyloxy, aralkylcarbonyloxy, alkoxycarbonyloxy, aryloxycarbon-
 yloxy, alkoxyaryloxy, aralkoxycarbonyloxy, ureido, alkylureido, aryl-
 ureido, amino, aminoalkyl, alkylaminoalkyl, dialkylaminoalkyl, aryl-
 aminoalkyl, diarylaminoalkyl, alkylarylaminominoalkyl, alkylamino, dialkyl-
 amino, haloalkylamino, haloalkylarylaminomino, arylamino, diarylamino, alkyl-
 15 arylamino, aralkylamino, alkylcarbonylamino, aralkylcarbonylamino,
 haloalkylcarbonylamino, alkoxycarbonylamino, aralkoxycarbonylamino,
 arylcarbonylamino, arylcarbonylaminoalkyl, aryloxycarbonylaminoalkyl,
 aryloxyarylcarbonylamino, aryloxycarbonylamino, alkylenedioxyalkyl,
 dialkylalkylenedioxyalkyl, alkylsulfonylamino, arylsulfonylamino, azido,
 20 dialkylphosphonyl, alkylarylphosphonyl, diarylphosphonyl, alkylthio, aryl-
 thio, perfluoroalkylthio, hydroxycarbonylalkylthio, thiocyno,
 isothiocyno, alkylsulfinyl, alkylsulfonyl, arylsulfinyl, arylsulfonyl,
 aminosulfonyl, alkylaminosulfonyl, dialkylaminosulfonyl,
 arylaminosulfonyl, diarylamino sulfonyl or alkylarylaminosulfonyl; or two
 25 Q¹ groups, which substitute atoms in a 1,2 or 1,3 arrangement, together
 form alkylenedioxy (*i.e.*, -O-(CH₂)_z-O-), thioalkylenoxy (*i.e.*,
 -S-(CH₂)_z-O-) or alkylenedithioxy (*i.e.*, -S-(CH₂)_z-S-) where z is 1 or 2; and
 each Q¹ is independently unsubstituted or substituted with one or
 more substituents, in one embodiment, one to three or four substituents,

-10-

each independently selected from Q^2 , where Q^2 is halo, pseudohalo, hydroxy, oxo, thia, nitrile, nitro, formyl, mercapto, amino, hydroxyalkyl, hydroxyaryl, hydroxycarbonyl, alkyl, haloalkyl, polyhaloalkyl, aminoalkyl, diaminoalkyl, alkenyl containing 1 to 2 double bonds, alkynyl containing
 5 1 to 2 triple bonds, cycloalkyl, heterocyclyl, aryl, heteroaryl, aralkyl, aralkenyl, aralkynyl, alkoxycarbonyl, aryloxycarbonyl, aralkoxycarbonyl, arylcarbonylalkyl, aminocarbonyl, alkoxy, aryloxy, aralkoxy, alkylenedioxy, amino, aminoalkyl, dialkylamino, arylamino, diarylamino, alkylamino, dialkylamino, haloalkylamino, arylamino, diarylamino, alkyl-
 10 arylamino, aralkylamino, alkoxycarbonylamino, arylcarbonylamino, alkylthio or arylthio.

In another embodiment, the compounds for use in the compositions and methods provided herein have formula I:



where R^1 is substituted or unsubstituted aryl, substituted or
 25 unsubstituted heteroaryl, substituted or unsubstituted aralkyl, substituted or unsubstituted heteroaralkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted cycloalkylalkyl, or substituted or unsubstituted heterocyclylalkyl; R^2 is hydrogen, substituted or unsubstituted alkyl, or substituted or
 30 unsubstituted aryl; R^3 is substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted aryl, or substituted or unsubstituted

-11-

heteroaryl; R^4 is halide, pseudohalide, $C(J)R^{30}$, $C(J)OR^{30}$, $C(J)NR^{31}R^{32}$, $CH_2NR^{31}R^{32}$, CH_2OR^{31} , $CR^{30}=CR^{31}R^{32}$, NO_2 or $NR^{31}R^{32}$; and R^5 is substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted aralkyl, substituted or unsubstituted aralkenyl, substituted or unsubstituted aralkynyl, substituted or unsubstituted heteroaralkyl, substituted or unsubstituted heteroaralkenyl, substituted or unsubstituted heteroaralkynyl, $-N=CR^6R^7$ or $-NR^9R^{10}$;

10 where R^6 and R^7 are each independently hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted aralkyl, or substituted or unsubstituted heteroaralkyl; or together form substituted or unsubstituted alkylene, substituted or unsubstituted alkenylene, substituted or unsubstituted alkynylene, or $-(CH_2)_xX(CH_2)_y-$ where x and y are each independently 1, 2 or 3, and X is O, S or NR^8 ;

15 R^8 is substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted alkylcarbonyl, substituted or unsubstituted arylcarbonyl, or substituted or unsubstituted heteroarylcarbonyl;

20 R^9 and R^{10} are each independently hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted aralkyl, or substituted or unsubstituted heteroaralkyl;

25 R^{30} is hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or

-12-

unsubstituted cycloalkyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted cycloalkylalkyl, substituted or unsubstituted heterocyclalkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted aralkyl, or substituted or unsubstituted heteroaralkyl;

- 5 R^{31} and R^{32} are each independently hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted cycloalkylalkyl, substituted or unsubstituted heterocyclalkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted aralkyl, substituted or unsubstituted heteroaralkyl, or $C(J)R^{35}$;

J is O, S or NR^{40} ;

- 15 R^{35} is hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted alkoxy, substituted or unsubstituted aralkoxy, substituted or unsubstituted alkylamino, substituted or unsubstituted dialkylamino, substituted or unsubstituted arylalkylamino, or substituted or unsubstituted diarylamino;

R^{40} is hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl;

- 25 where the alkyl, alkenyl, alkynyl, cycloalkyl, heterocyclyl, alkylene, alkenylene, alkynylene, aryl, heteroaryl, aralkyl, aralkenyl, aralkynyl, heteroaralkyl, heteroaralkenyl and heteroaralkynyl moieties of R^1 , R^2 , R^3 , R^5 , R^6 , R^7 , R^8 , R^9 and R^{10} are unsubstituted or substituted with one or more substituents, in one embodiment, one to three or four substituents,

-13-

each independently selected from Q^1 , where Q^1 is halo, pseudohalo, hydroxy, oxo, thia, nitrile, nitro, formyl, mercapto, hydroxycarbonyl, hydroxycarbonylalkyl, alkyl, haloalkyl, polyhaloalkyl, aminoalkyl, diaminoalkyl, alkenyl containing 1 to 2 double bonds, alkynyl containing

5 1 to 2 triple bonds, cycloalkyl, cycloalkylalkyl, heterocyclyl, heterocyclylalkyl, aryl, heteroaryl, aralkyl, aralkenyl, aralkynyl, heteroarylalkyl, trialkylsilyl, dialkylarylsilyl, alkyl diarylsilyl, triarylsilyl, alkylidene, arylalkylidene, alkylcarbonyl, arylcarbonyl, heteroarylcarbonyl, alkoxycarbonyl, alkoxycarbonylalkyl, aryloxy carbonyl, aryloxy carbonyl-

10 alkyl, aralkoxycarbonyl, aralkoxycarbonylalkyl, arylcarbonylalkyl, aminocarbonyl, alkylaminocarbonyl, dialkylaminocarbonyl, arylaminocarbonyl, diarylaminocarbonyl, arylalkylaminocarbonyl, alkoxy, aryloxy, perfluoroalkoxy, alkenyloxy, alkynyloxy, aralkoxy, alkylcarbonyloxy, arylcarbonyloxy, aralkylcarbonyloxy, alkoxycarbonyloxy, aryloxy carbony-

15 loxy, aralkoxycarbonyloxy, ureido, alkylureido, arylureido, amino, aminoalkyl, alkylaminoalkyl, dialkylaminoalkyl, arylaminoalkyl, diarylaminoalkyl, alkylarylaminalkyl, alkylamino, dialkylamino, haloalkylamino, arylamino, diarylamino, alkylarylamino, alkylcarbonylamino, alkoxycarbonylamino, aralkoxycarbonylamino, arylcarbonylamino,

20 arylcarbonylaminoalkyl, aryloxy carbonylaminoalkyl, aryloxyarylcarbonylamino, aryloxy carbonylamino, alkylsulfonylamino, arylsulfonylamino, azido, dialkylphosphonyl, alkylarylphosphonyl, diarylphosphonyl, alkylthio, arylthio, perfluoroalkylthio, hydroxycarbonylalkylthio, thiocyano, isothiocyano, alkylsulfinyl, alkylsulfonyl, arylsulfinyl, arylsul-

25 fonyl, aminosulfonyl, alkylaminosulfonyl, dialkylaminosulfonyl, arylaminosulfonyl, diarylaminosulfonyl or alkylarylaminosulfonyl; or two Q^1 groups, which substitute atoms in a 1,2 or 1,3 arrangement, together form alkylenedioxy (*i.e.*, $-O-(CH_2)_z-O-$), thioalkylenoxy (*i.e.*, $-S-(CH_2)_z-O-$) or alkylenedithioxy (*i.e.*, $-S-(CH_2)_z-S-$) where z is 1 or 2; and

-14-

the aryl and heteroaryl groups of Q^1 are unsubstituted or substituted with one or more substituents, in one embodiment, one to three or four substituents, each independently selected from Q^2 , where Q^2 is alkyl, halo, pseudohalo, alkoxy, aryloxy or alkylenedioxy.

5 In certain embodiments, R^2 is hydrogen, or is substituted or unsubstituted alkyl. In other embodiments, R^2 is hydrogen.

In another embodiment, R^3 is substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, or substituted or unsubstituted alkynyl. In another embodiment, R^3 is substituted or unsubstituted alkyl.

10 In another embodiment, R^3 is haloalkyl. In other embodiments, R^3 is lower haloalkyl. In another embodiment, R^3 is lower perfluoroalkyl. In another embodiment, R^3 is trifluoromethyl or pentafluoroethyl. In another embodiment, R^3 is trifluoromethyl.

In other embodiments, R^4 is pseudohalide. In another embodiment,
15 R^4 is cyano.

In another embodiment, R^6 and R^7 are selected with the proviso that (i) they are not both methyl; and (ii) they do not together form pentylene (*i.e.*, $-(CH_2)_5-$).

The groups R^1 , R^2 , R^3 , R^4 , R^5 , R^6 , R^7 , R^8 , R^9 , R^{10} , Q^1 and Q^2 are
20 selected such that the resulting compound has nuclear receptor modulation activity, such as in at least one assay described herein, including LXR or orphan nuclear receptor modulation activity, such as LXR antagonist or agonist activity. In certain embodiments, the compounds provided herein have an IC_{50} and/or EC_{50} of less than about
25 $100\ \mu M$ in a $LXR\alpha$ or $LXR\beta$ binding or co-transfection assay. The $LXR\alpha$ or $LXR\beta$ IC_{50} and/or EC_{50} values for the compounds provided herein are, in certain embodiments, less than about $50\ \mu M$, $25\ \mu M$, $10\ \mu M$, $1\ \mu M$, $100\ nM$, $10\ nM$ or $1\ nM$ in binding or co-transfection assays. In certain of these embodiments, the compounds provided herein are LXR agonists.

-15-

In other of these embodiments, the compounds provided herein are LXR antagonists. In other embodiments, the compounds provided herein exhibit a % efficacy relative to standard (N-(3-((4-fluorophenyl)-(naphthalene-2-sulfonyl)amino)propyl)-2,2-dimethylpropionamide) of
5 greater than about 50%, 60%, 70%, 80%, 90%, 100%, 110%, 120%, 130%, 140% or more in a co-transfection assay.

Also of interest are any pharmaceutically-acceptable derivatives, including salts, esters, enol ethers, enol esters, solvates, hydrates and prodrugs of the compounds described herein. Pharmaceutically-accept-
10 able salts, include, but are not limited to, amine salts, such as but not limited to N,N'-dibenzylethylenediamine, chlorprocaine, choline, ammonia, diethanolamine and other hydroxyalkylamines, ethylenediamine, N-methylglucamine, procaine, N-benzylphenethylamine, 1-para-chlorobenzyl-2-pyrrolidin-1'-ylmethylbenzimidazole, diethylamine
15 and other alkylamines, piperazine and tris(hydroxymethyl)aminomethane; alkali metal salts, such as but not limited to lithium, potassium and sodium; alkali earth metal salts, such as but not limited to barium, calcium and magnesium; transition metal salts, such as but not limited to zinc, aluminum, and other metal salts, such as but not limited to sodium
20 hydrogen phosphate and disodium phosphate; and also including, but not limited to, salts of mineral acids, such as but not limited to hydrochlorides and sulfates; and salts of organic acids, such as but not limited to acetates, lactates, malates, tartrates, citrates, ascorbates, succinates, butyrates, valerates and fumarates.

25 Pharmaceutical compositions formulated for administration by an appropriate route and means containing effective concentrations of one or more of the compounds provided herein, or pharmaceutically acceptable derivatives thereof, that deliver amounts effective for the treatment, prevention, or amelioration of one or more symptoms of

-16-

diseases or disorders that are modulated or otherwise affected by nuclear receptor activity, including LXR and/or orphan nuclear receptor activity, or in which nuclear receptor activity, including LXR and/or orphan nuclear receptor activity, is implicated, are also provided. The effective amounts
5 and concentrations are effective for ameliorating any of the symptoms of any of the diseases or disorders.

Methods for treatment, prevention, or amelioration of one or more symptoms of diseases or disorders mediated by or in which nuclear receptor activity, including LXR and/or orphan nuclear receptor activity,
10 is implicated, are provided. Such methods include methods of treatment, prevention and amelioration of one or more symptoms of hypercholesterolemia, hyperlipoproteinemia, hypertriglyceridemia, lipodystrophy, hyperglycemia, diabetes mellitus, dyslipidemia, atherosclerosis, gallstone disease, acne vulgaris, acneiform skin
15 conditions, diabetes, Parkinson's disease, cancer, Alzheimer's disease, inflammation, immunological disorders, lipid disorders, obesity, conditions characterized by a perturbed epidermal barrier function, conditions of disturbed differentiation or excess proliferation of the epidermis or mucous membrane, or cardiovascular disorders, using one or more of the
20 compounds provided herein, or pharmaceutically acceptable derivatives thereof.

Methods of modulating the activity of nuclear receptors, including LXR and/or orphan nuclear receptors, using the compounds and compositions provided herein are also provided. The compounds and
25 compositions provided herein are active in assays, such as the assays provided herein, that measure the activity of nuclear receptors, including LXR and/or orphan nuclear receptors. These methods include inhibiting and up-regulating the activity of nuclear receptors, including LXR and/or orphan nuclear receptors.

-17-

Methods of reducing cholesterol levels in a subject in need thereof by administration of one or more compounds or compositions provided herein are also provided.

5 Methods of modulating cholesterol metabolism using the compounds and compositions provided herein are provided.

Methods of treating, preventing, or ameliorating one or more symptoms of diseases or disorders which are affected by cholesterol, triglyceride, or bile acid levels by administration of one or more of the compounds and compositions provided herein are also provided.

10 Methods of raising the plasma level of high density lipoprotein (HDL) by administration of one or more compounds and compositions provided herein are also provided.

In practicing the methods, effective amounts of the compounds or compositions containing therapeutically effective concentrations of the
15 compounds, which are formulated for systemic delivery, including parenteral, oral, or intravenous delivery, or for local or topical application, for the treatment of nuclear receptor, including LXR and/or orphan nuclear receptor, mediated diseases or disorders, or diseases or disorders in which nuclear receptor activity, including LXR and/or orphan nuclear
20 receptor activity, is implicated, including, but not limited to, hypercholesterolemia, hyperlipoproteinemia, hypertriglyceridemia, lipodystrophy, hyperglycemia, diabetes mellitus, dyslipidemia, atherosclerosis, gallstone disease, acne vulgaris, acneiform skin conditions, diabetes, Parkinson's disease, cancer, Alzheimer's disease,
25 inflammation, immunological disorders, lipid disorders, obesity, conditions characterized by a perturbed epidermal barrier function, conditions of disturbed differentiation or excess proliferation of the epidermis or mucous membrane, or cardiovascular disorders, are administered to an individual exhibiting the symptoms of these diseases or disorders. The

-18-

amounts are effective to ameliorate or eliminate one or more symptoms of the diseases or disorders.

Articles of manufacture containing packaging material, a compound or composition, or pharmaceutically acceptable derivative thereof, provided herein, which is effective for modulating the activity of nuclear receptors, including LXR and/or orphan nuclear receptors, or for treatment, prevention or amelioration of one or more symptoms of nuclear receptor, including LXR and/or orphan nuclear receptor, mediated diseases or disorders, or diseases or disorders in which nuclear receptor activity, including LXR and/or orphan nuclear receptor activity, is implicated, within the packaging material, and a label that indicates that the compound or composition, or pharmaceutically acceptable derivative thereof, is used for modulating the activity of nuclear receptors, including LXR and/or orphan nuclear receptors, or for treatment, prevention or amelioration of one or more symptoms of nuclear receptor, including LXR and/or orphan nuclear receptor, mediated diseases or disorders, or diseases or disorders in which nuclear receptor activity, including LXR and/or orphan nuclear receptor activity, is implicated, are provided.

BRIEF DESCRIPTION OF DRAWINGS

Figure 1 provides in vitro data for the compounds whose synthesis is described in the Examples. Data is provided for LXR α and LXR β receptors. Average EC₅₀ ("EC50_AVG") for LXR agonism is provided as follows: I = 0.0001-0.01 μ M, II = 0.01-0.1 μ M, III = 0.1-1.0 μ M, IV = 1.0-10.0 μ M and NC = Not Calculated. Average percent efficacy ("EFF_AVG") for LXR agonism relative to control (N-(3-((4-fluoro-phen-yl)-(naphthalene-2-sulfonyl)-amino)propyl)-2,2-dimethylpropionamide) is provided as follows: A = 0-50%, B = 50-100%, C = 100-150%, D > 150% and NC = Not Calculated. Average Ki is provided as follows: A1 = 0.0001-0.1 μ M, B1 = 0.1-1 μ M, C1 = 1-2 μ M, D1 = >2 μ M.

DETAILED DESCRIPTION OF PREFERRED EMBODIMENTS

A. Definitions

Unless defined otherwise, all technical and scientific terms used herein have the same meaning as is commonly understood by one of
5 ordinary skill in the art to which this invention belongs. All patents, applications, published applications and other publications are incorporated by reference in their entirety. In the event that there are a plurality of definitions for a term herein, those in this section prevail unless stated otherwise.

10 As used herein, a nuclear receptor is a member of a superfamily of regulatory proteins that are receptors for, *e.g.*, steroids, retinoids, vitamin D and thyroid hormones. These proteins bind to cis-acting elements in the promoters of their target genes and modulate gene expression in response to a ligand therefor. Nuclear receptors may be classified based
15 on their DNA binding properties. For example, the glucocorticoid, estrogen, androgen, progestin and mineralocorticoid receptors bind as homodimers to hormone response elements (HREs) organized as inverted repeats. Another example are receptors, including those activated by retinoic acid, thyroid hormone, vitamin D₃, fatty acids/peroxisome
20 proliferators and ecdysone, that bind to HREs as heterodimers with a common partner, the retinoid X receptor (RXR). Among the latter receptors is LXR.

As used herein, an orphan nuclear receptor is a nuclear receptor for which the natural ligand is unknown.

25 As used herein, liver X receptor or LXR refers to a nuclear receptor implicated in cholesterol biosynthesis. As used herein, the term LXR refers to both LXR α and LXR β , two forms of the protein found in mammals. Liver X receptor- α or LXR α refers to the receptor described in U.S. Patent Nos. 5,571,696, 5,696,233 and 5,710,004, and Willy *et al.*

-20-

(1995) *Gene Dev.* 9(9):1033-1045. Liver X receptor- β or LXR β refers to the receptor described in Peet *et al.* (1998) *Curr. Opin. Genet. Dev.* 8(5):571-575; Song *et al.* (1995) *Ann. N.Y. Acad. Sci.* 761:38-49; Alberti *et al.* (2000) *Gene* 243(1-2):93-103; and references cited therein;
5 and in U.S. Patent Nos. 5,571,696, 5,696,233 and 5,710,004.

Diabetes mellitus, commonly called diabetes, refers to a disease process derived from multiple causative factors and characterized by elevated levels of plasma glucose, referred to as hyperglycemia. See, e.g., LeRoith, D. et al., (eds.), DIABETES MELLITUS (Lippincott-Raven
10 Publishers, Philadelphia, Pa. U.S.A. 1996). According to the American Diabetes Association, diabetes mellitus is estimated to affect approximately 6% of the world population. Uncontrolled hyperglycemia is associated with increased and premature mortality due to an increased risk for macrovascular and macrovascular diseases, including
15 nephropathy, neuropathy, retinopathy, hypertension, cerebrovascular disease and coronary heart disease. Therefore, control of glucose homeostasis is a critically important approach for the treatment of diabetes.

There are two major forms of diabetes: type 1 diabetes (formerly
20 referred to as insulin-dependent diabetes or IDDM); and type 2 diabetes (formerly referred to as noninsulin dependent diabetes or NIDDM).

Type 2 diabetes is a disease characterized by insulin resistance accompanied by relative, rather than absolute, insulin deficiency. Type 2 diabetes can range from predominant insulin resistance with relative
25 insulin deficiency to predominant insulin deficiency with some insulin resistance. Insulin resistance is the diminished ability of insulin to exert its biological action across a broad range of concentrations. In insulin resistant individuals, the body secretes abnormally high amounts of insulin to compensate for this defect. When inadequate amounts of

-21-

insulin are present to compensate for insulin resistance and adequate control of glucose, a state of impaired glucose tolerance develops. In a significant number of individuals, insulin secretion declines further and the plasma glucose level rises, resulting in the clinical state of diabetes.

- 5 Type 2 diabetes can be due to a profound resistance to insulin stimulating regulatory effects on glucose and lipid metabolism in the main insulin-sensitive tissues: muscle, liver and adipose tissue. This resistance to insulin responsiveness results in insufficient insulin activation of glucose uptake, oxidation and storage in muscle and inadequate insulin
- 10 repression of lipolysis in adipose tissue and of glucose production and secretion in liver. In Type 2 diabetes, free fatty acid levels are often elevated in obese and some non-obese patients and lipid oxidation is increased.

- Premature development of atherosclerosis and increased rate of
- 15 cardiovascular and peripheral vascular diseases are characteristic features of patients with diabetes. Hyperlipidemia is an important precipitating factor for these diseases. Hyperlipidemia is a condition generally characterized by an abnormal increase in serum lipids in the bloodstream and is an important risk factor in developing atherosclerosis and heart
- 20 disease. For a review of disorders of lipid metabolism, see, e.g., Wilson, J. et al., (ed.), Disorders of Lipid Metabolism, Chapter 23, Textbook of Endocrinology, 9th Edition, (W. B. Sanders Company, Philadelphia, Pa. U.S.A. 1998). Hyperlipidemia is usually classified as primary or secondary hyperlipidemia. Primary hyperlipidemia is generally caused by
- 25 genetic defects, while secondary hyperlipidemia is generally caused by other factors, such as various disease states, drugs, and dietary factors. Alternatively, hyperlipidemia can result from both a combination of primary and secondary causes of hyperlipidemia. Elevated cholesterol levels are associated with a number of disease states, including coronary

-22-

artery disease, angina pectoris, carotid artery disease, strokes, cerebral arteriosclerosis, and xanthoma.

Dyslipidemia, or abnormal levels of lipoproteins in blood plasma, is a frequent occurrence among diabetics, and has been shown to be one of the main contributors to the increased incidence of coronary events and deaths among diabetic subjects (see, e.g., Joslin, E. Ann. Chim. Med. (1927) 5: 1061-1079). Epidemiological studies since then have confirmed the association and have shown a several-fold increase in coronary deaths among diabetic subjects when compared with nondiabetic subjects (see, e.g., Garcia, M. J. et al., Diabetes (1974) 23: 105-11 (1974); and Laakso, M. and Lehto, S., Diabetes Reviews (1997) 5(4): 294-315). Several lipoprotein abnormalities have been described among diabetic subjects (Howard B., et al., Arteriosclerosis (1978) 30: 153-162).

The term "insulin resistance" can be defined generally as a disorder of glucose metabolism. More specifically, insulin resistance can be defined as the diminished ability of insulin to exert its biological action across a broad range of concentrations producing less than the expected biologic effect. (see, e.g., Reaven, G. M., J. Basic & Clin. Phys. & Pharm. (1998) 9: 387-406 and Flier, J. Ann Rev. Med. (1983) 34:145-60). Insulin resistant persons have a diminished ability to properly metabolize glucose and respond poorly, if at all, to insulin therapy. Manifestations of insulin resistance include insufficient insulin activation of glucose uptake, oxidation and storage in muscle and inadequate insulin repression of lipolysis in adipose tissue and of glucose production and secretion in liver. Insulin resistance can cause or contribute to polycystic ovarian syndrome, Impaired Glucose Tolerance (IGT), gestational diabetes, hypertension, obesity, atherosclerosis and a variety of other disorders. Eventually, the insulin resistant individuals can

-23-

progress to a point where a diabetic state is reached. The association of insulin resistance with glucose intolerance, an increase in plasma triglyceride and a decrease in high-density lipoprotein cholesterol concentrations, high blood pressure, hyperuricemia, smaller denser low-density lipoprotein particles, and higher circulating levels of plasminogen activator inhibitor-1), has been referred to as "Syndrome X" (see, e.g., Reaven, G. M., *Physiol. Rev.* (1995) 75: 473-486).

The term "diabetes mellitus" or "diabetes" means a disease or condition that is generally characterized by metabolic defects in production and utilization of glucose which result in the failure to maintain appropriate blood sugar levels in the body. The result of these defects is elevated blood glucose, referred to as "hyperglycemia." Type 2 diabetes often occurs in the face of normal, or even elevated, levels of insulin and can result from the inability of tissues to respond appropriately to insulin. Most type 2 diabetic patients are insulin resistant and have a relative deficiency of insulin, in that insulin secretion can not compensate for the resistance of peripheral tissues to respond to insulin. In addition, many type 2 diabetics are obese. Other types of disorders of glucose homeostasis include Impaired Glucose Tolerance, which is a metabolic stage intermediate between normal glucose homeostasis and diabetes, and Gestational Diabetes Mellitus, which is glucose intolerance in pregnancy in women with no previous history of type 1 or type 2 diabetes.

The term "complication" of diabetes includes, but is not limited to, microvascular complications and macrovascular complications. Microvascular complications are those complications which generally result in small blood vessel damage. These complications include, e.g., retinopathy (the impairment or loss of vision due to blood vessel damage in the eyes); neuropathy (nerve damage and foot problems due to blood

-24-

vessel damage to the nervous system); and nephropathy (kidney disease due to blood vessel damage in the kidneys). macrovascular complications are those complications which generally result from large blood vessel damage. These complications include, e.g., cardiovascular disease and peripheral vascular disease. Cardiovascular disease refers to diseases of blood vessels of the heart. See, e.g., Kaplan, R. M., et al., "Cardiovascular diseases" in HEALTH AND HUMAN BEHAVIOR, pp. 206-242 (McGraw-Hill, New York 1993). Cardiovascular disease is generally one of several forms, including, e.g., hypertension (also referred to as high blood pressure), coronary heart disease, stroke, and rheumatic heart disease. Peripheral vascular disease refers to diseases of any of the blood vessels outside of the heart. It is often a narrowing of the blood vessels that carry blood to leg and arm muscles.

The term "hyperlipidemia" refers to the presence of an abnormally elevated level of lipids in the blood. Hyperlipidemia can appear in at least three forms: (1) hypercholesterolemia, i.e., an elevated cholesterol level; (2) hypertriglyceridemia, i.e., an elevated triglyceride level; and (3) combined hyperlipidemia, i.e., a combination of hypercholesterolemia and hypertriglyceridemia.

The term "dyslipidemia" refers to abnormal levels of lipoproteins in blood plasma including both depressed and/or elevated levels of lipoproteins (e.g., elevated levels of LDL, VLDL and depressed levels of HDL).

Exemplary Primary Hyperlipidemia include, but are not limited to, the following: (1) Familial Hyperchylomicronemia, a rare genetic disorder which causes a deficiency in an enzyme, LP lipase, that breaks down fat molecules. The LP lipase deficiency can cause the accumulation of large quantities of fat or lipoproteins in the blood;

-25-

(2) Familial Hypercholesterolemia, a relatively common genetic disorder caused where the underlying defect is a series of mutations in the LDL receptor gene that result in malfunctioning LDL receptors and/or absence of the LDL receptors. This brings about ineffective clearance of
5 LDL by the LDL receptors resulting in elevated LDL and total cholesterol levels in the plasma;

(3) Familial Combined Hyperlipidemia, also known as multiple lipoprotein-type hyperlipidemia; an inherited disorder where patients and their affected first-degree relatives can at various times manifest high
10 cholesterol and high triglycerides. Levels of HDL cholesterol are often moderately decreased;

(4) Familial Defective Apolipoprotein B-100 is a relatively common autosomal dominant genetic abnormality. The defect is caused by a single nucleotide mutation that produces a substitution of glutamine for
15 arginine which can cause reduced affinity of LDL particles for the LDL receptor. Consequently, this can cause high plasma LDL and total cholesterol levels;

(5) Familial Dysbetalipoproteinemia, also referred to as Type III Hyperlipoproteinemia, is an uncommon inherited disorder resulting in
20 moderate to severe elevations of serum TG and cholesterol levels with abnormal apolipoprotein E function. HDL levels are usually normal; and

(6) Familial Hypertriglyceridemia, is a common inherited disorder in which the concentration of plasma VLDL is elevated. This can cause mild to moderately elevated triglyceride levels (and usually not
25 cholesterol levels) and can often be associated with low plasma HDL levels.

Risk factors in exemplary Secondary Hyperlipidemia include, but are not limited to, the following: (1) disease risk factors, such as a history of type 1 diabetes, type 2 diabetes, Cushing's syndrome,

-26-

hypothyroidism and certain types of renal failure; (2) drug risk factors, which include, birth control pills; hormones, such as estrogen, and corticosteroids; certain diuretics; and various β -blockers; (3) dietary risk factors include dietary fat intake per total calories greater than 40%;
5 saturated fat intake per total calories greater than 10%; cholesterol intake greater than 300 mg per day; habitual and excessive alcohol use; and obesity; and (4) non-genetic dyslipidemias.

The terms "obese" and "obesity" refers to, according to the World Health Organization, a Body Mass Index (BMI) greater than 27.8 kg/m²
10 for men and 27.3 kg/m² for women (BMI equals weight (kg)/height (m²). Obesity is linked to a variety of medical conditions including diabetes and hyperlipidemia. Obesity is also a known risk factor for the development of type 2 diabetes (See, e.g., Barrett-Conner, E., *Epidemol. Rev.* (1989) 11: 172-181; and Knowler, et al., *Am. J Clin. Nutr.* (1991) 53:1543-
15 1551).

As used herein, pharmaceutically acceptable derivatives of a compound include salts, esters, enol ethers, enol esters, acetals, ketals, hemiacetals, hemiketals, acids, bases, solvates, hydrates or prodrugs thereof. Such derivatives may be readily prepared by those of skill in this
20 art using known methods for such derivatization. The compounds produced may be administered to animals or humans without substantial toxic effects and either are pharmaceutically active or are prodrugs. Pharmaceutically acceptable salts include, but are not limited to, amine salts, such as but not limited to N,N'-dibenzylethylenediamine,
25 chloroprocaine, choline, ammonia, diethanolamine and other hydroxyalkylamines, ethylenediamine, N-methylglucamine, procaine, N-benzylphenethylamine, 1-para-chlorobenzyl-2-pyrrolidin-1'-ylmethylbenzimidazole, diethylamine and other alkylamines, piperazine and tris(hydroxymethyl)aminomethane; alkali metal salts, such as but not

-27-

limited to lithium, potassium and sodium; alkali earth metal salts, such as but not limited to barium, calcium and magnesium; transition metal salts, such as but not limited to zinc; and other metal salts, such as but not limited to sodium hydrogen phosphate and disodium phosphate; and also
5 including, but not limited to, salts of mineral acids, such as but not limited to hydrochlorides and sulfates; and salts of organic acids, such as but not limited to acetates, lactates, malates, tartrates, citrates, ascorbates, succinates, butyrates, valerates and fumarates.

Pharmaceutically acceptable esters include, but are not limited to, alkyl,
10 alkenyl, alkynyl, aryl, heteroaryl, aralkyl, heteroaralkyl, cycloalkyl and heterocyclyl esters of acidic groups, including, but not limited to; carboxylic acids, phosphoric acids, phosphinic acids, sulfonic acids, sulfinic acids and boronic acids. Pharmaceutically acceptable enol ethers include, but are not limited to, derivatives of formula $C=C(OR)$ where R
15 is hydrogen, alkyl, alkenyl, alkynyl, aryl, heteroaryl, aralkyl, heteroaralkyl, cycloalkyl or heterocyclyl. Pharmaceutically acceptable enol esters include, but are not limited to, derivatives of formula $C=C(OC(O)R)$ where R is hydrogen, alkyl, alkenyl, alkynyl, aryl, heteroaryl, aralkyl, heteroaralkyl, cycloalkyl or heterocyclyl. Pharmaceutically acceptable
20 solvates and hydrates are complexes of a compound with one or more solvent or water molecules, or 1 to about 100, or 1 to about 10, or one to about 2, 3 or 4, solvent or water molecules.

As used herein, treatment means any manner in which one or more of the symptoms of a disease or disorder are ameliorated or
25 otherwise beneficially altered. Treatment also encompasses any pharmaceutical use of the compositions herein, such as use for treating a nuclear receptor, including LXR and/or orphan nuclear receptor, mediated diseases or disorders, or diseases or disorders in which nuclear receptor

-28-

activity, including LXR and/or orphan nuclear receptor activity, is implicated.

As used herein, amelioration of the symptoms of a particular disorder by administration of a particular compound or pharmaceutical composition refers to any lessening, whether permanent or temporary,
5 lasting or transient that can be attributed to or associated with administration of the composition.

The term "modulate" refers to the treating, prevention, suppression, enhancement or induction of a function or condition. For
10 example, the compounds claimed herein, can modulate hyperlipidemia by lowering cholesterol in a human, thereby suppressing hyperlipidemia.

As used herein, the IC_{50} refers to an amount, concentration or dosage of a particular test compound that achieves a 50% inhibition of a maximal response, such as modulation of LXR activity, in an assay that
15 measures such response.

As used herein, EC_{50} refers to a dosage, concentration or amount of a particular test compound that elicits a dose-dependent response at 50% of maximal expression of a particular response that is induced, provoked or potentiated by the particular test compound.

20 The term "cholesterol" refers to a steroid alcohol that is an essential component of cell membranes and myelin sheaths and, as used herein, incorporates its common usage. Cholesterol also serves as a precursor for steroid hormones and bile acids.

The term "triglyceride(s)" ("TGs"), as used herein, incorporates its
25 common usage. TGs consist of three fatty acid molecules esterified to a glycerol molecule and serve to store fatty acids which are used by muscle cells for energy production or are taken up and stored in adipose tissue.

-29-

As used herein, a prodrug is a compound that, upon *in vivo* administration, is metabolized by one more steps or processes or otherwise converted to the biologically, pharmaceutically or therapeutically active form of the compound. To produce a prodrug, the pharmaceutically active compound is modified such that the active compound will be regenerated by metabolic processes. The prodrug may be designed to alter the metabolic stability or the transport characteristics of a drug, to mask side effects or toxicity, to improve the flavor of a drug or to alter other characteristics or properties of a drug.

By virtue of knowledge of pharmacodynamic processes and drug metabolism *in vivo*, those of skill in this art, once a pharmaceutically active compound is known, can design prodrugs of the compound (see, *e.g.*, Nogrady (1985) *Medicinal Chemistry A Biochemical Approach*, Oxford University Press, New York, pages 388-392).

It is to be understood that the compounds provided herein may contain chiral centers. Such chiral centers may be of either the (R) or (S) configuration, or may be a mixture thereof. Thus, the compounds provided herein may be enantiomerically pure, or be stereoisomeric or diastereomeric mixtures. The compounds provided herein include all possible isomers, as well as, their racemic and optically pure forms. Optically active (+) and (-), (r)- and (S)-, or (D)- and (L)-isomers may be prepared using chiral synthons or chiral reagents, or resolved using conventional techniques, such as reverse phase HPLC. When the compounds described herein contain olefinic double bonds or other centers of geometric asymmetry, and unless specified otherwise, it is intended that the compounds include both E and Z geometric isomers. Likewise, all tautomeric forms are also intended to be included. In the case of amino acid residues, such residues may be of either the L- or D-form. The configuration for naturally occurring amino acid residues is

-30-

generally L. When not specified the residue is the L form. As used herein, the term "amino acid" refers to α -amino acids which are racemic, or of either the D- or L-configuration. The designation "d" preceding an amino acid designation (*e.g.*, dAla, dSer, dVal, etc.) refers to the D-isomer of the amino acid. The designation "dl" preceding an amino acid designation (*e.g.*, dlPip) refers to a mixture of the L- and D-isomers of the amino acid. It is to be understood that the chiral centers of the compounds provided herein may undergo epimerization *in vivo*. As such, one of skill in the art will recognize that administration of a compound in its (R) form is equivalent, for compounds that undergo epimerization *in vivo*, to administration of the compound in its (S) form.

As used herein, substantially pure means sufficiently homogeneous to appear free of readily detectable impurities as determined by standard methods of analysis, such as thin layer chromatography (TLC), gel electrophoresis, high performance liquid chromatography (HPLC) and mass spectrometry (MS), used by those of skill in the art to assess such purity, or sufficiently pure such that further purification would not detectably alter the physical and chemical properties, such as enzymatic and biological activities, of the substance. Methods for purification of the compounds to produce substantially chemically pure compounds are known to those of skill in the art. A substantially chemically pure compound may, however, be a mixture of stereoisomers. In such instances, further purification might increase the specific activity of the compound.

As used herein, the nomenclature alkyl, alkoxy, carbonyl, *etc.* is used as is generally understood by those of skill in this art.

As used herein, alkyl, alkenyl and alkynyl carbon chains, if not specified, contain from 1 to 20 carbons, or 1 to 16 carbons, and are straight or branched. Alkenyl carbon chains of from 2 to 20 carbons, in

-31-

certain embodiments, contain 1 to 8 double bonds, and the alkenyl carbon chains of 2 to 16 carbons, in certain embodiments, contain 1 to 5 double bonds. Alkynyl carbon chains of from 2 to 20 carbons, in certain embodiments, contain 1 to 8 triple bonds, and the alkynyl carbon chains of 2 to 16 carbons, in certain embodiments, contain 1 to 5 triple bonds. Exemplary alkyl, alkenyl and alkynyl groups herein include, but are not limited to, methyl, ethyl, propyl, isopropyl, isobutyl, n-butyl, sec-butyl, tert-butyl, isopentyl, neopentyl, tert-pentylyl and isohexyl. As used herein, lower alkyl, lower alkenyl, and lower alkynyl refer to carbon chains having less than about 6 carbons. As used herein, "alk(en)(yn)yl" refers to an alkyl group containing at least one double bond and at least one triple bond.

As used herein, "cycloalkyl" refers to a saturated mono- or multi-cyclic ring system, in certain embodiments of 3 to 10 carbon atoms, in other embodiments of 3 to 6 carbon atoms; cycloalkenyl and cycloalkynyl refer to mono- or multicyclic ring systems that respectively include at least one double bond and at least one triple bond. Cycloalkenyl and cycloalkynyl groups may, in certain embodiments, contain 3 to 10 carbon atoms, with cycloalkenyl groups, in further embodiments, containing 4 to 7 carbon atoms and cycloalkynyl groups, in further embodiments, containing 8 to 10 carbon atoms. The ring systems of the cycloalkyl, cycloalkenyl and cycloalkynyl groups may be composed of one ring or two or more rings which may be joined together in a fused, bridged or spiro-connected fashion. "Cycloalk(en)(yn)yl" refers to a cycloalkyl group containing at least one double bond and at least one triple bond.

As used herein, "substituted alkyl," "substituted alkenyl," "substituted alkynyl," "substituted cycloalkyl," "substituted cycloalkenyl," and "substituted cycloalkynyl" refer to alkyl, alkenyl, alkynyl,

-32-

cycloalkyl, cycloalkenyl and cycloalkynyl groups, respectively, that are substituted with one or more substituents, in certain embodiments one to three substituents.

As used herein, "aryl" refers to aromatic monocyclic or multicyclic groups containing from 6 to 19 carbon atoms. Aryl groups include, but are not limited to groups such as fluorenyl, substituted fluorenyl, phenyl, substituted phenyl, naphthyl and substituted naphthyl.

As used herein, "heteroaryl" refers to a monocyclic or multicyclic aromatic ring system, in certain embodiments, of about 5 to about 15 members where one or more, in one embodiment 1 to 3, of the atoms in the ring system is a heteroatom, that is, an element other than carbon, including but not limited to, nitrogen, oxygen or sulfur. The heteroaryl group may be optionally fused to a benzene ring. Heteroaryl groups include, but are not limited to, furyl, imidazolyl, pyrrolidinyl, pyrimidinyl, tetrazolyl, thienyl, pyridyl, pyrrolyl, N-methylpyrrolyl, quinolinyl and isoquinolinyl.

As used herein, a "heteroarylium" group is a heteroaryl group that is positively charged on one or more of the heteroatoms.

As used herein, "heterocyclyl" refers to a monocyclic or multicyclic non-aromatic ring system, in one embodiment of 3 to 10 members, in another embodiment of 4 to 7 members, in a further embodiment of 5 to 6 members, where one or more, in certain embodiments, 1 to 3, of the atoms in the ring system is a heteroatom, that is, an element other than carbon, including but not limited to, nitrogen, oxygen or sulfur.

As used herein, "substituted aryl," "substituted heteroaryl" and "substituted heterocyclyl" refer to aryl, heteroaryl and heterocyclyl groups, respectively, that are substituted with one or more substituents, in certain embodiments one to three substituents.

-33-

As used herein, "aralkyl" refers to an alkyl group in which one of the hydrogen atoms of the alkyl is replaced by an aryl group.

As used herein, "heteroaralkyl" refers to an alkyl group in which one of the hydrogen atoms of the alkyl is replaced by a heteroaryl group.

5 As used herein, "halo", "halogen" or "halide" refers to F, Cl, Br or I.

As used herein, pseudohalides or pseudohalo groups are groups that behave substantially similar to halides. Such compounds can be used in the same manner and treated in the same manner as halides.

10 Pseudohalides include, but are not limited to, cyanide, cyanate, thiocyanate, selenocyanate, trifluoromethoxy, and azide.

As used herein, "haloalkyl" refers to an alkyl group in which one or more of the hydrogen atoms are replaced by halogen. Such groups include, but are not limited to, chloromethyl, trifluoromethyl and
15 1-chloro-2-fluoroethyl.

As used herein, "haloalkoxy" refers to RO- in which R is a haloalkyl group.

As used herein, "sulfinyl" or "thionyl" refers to -S(O)-. As used herein, "sulfonyl" or "sulfuryl" refers to -S(O)₂-. As used herein, "sulfo"
20 refers to -S(O)₂O-.

As used herein, "carboxy" refers to a divalent radical, -C(O)O-.

As used herein, "aminocarbonyl" refers to -C(O)NH₂.

As used herein, "alkylaminocarbonyl" refers to -C(O)NHR in which R is alkyl, including lower alkyl. As used herein, "dialkylaminocarbonyl"
25 refers to -C(O)NR'R in which R' and R are independently alkyl, including lower alkyl; "carboxamide" refers to groups of formula -NR'COR in which R' and R are independently alkyl, including lower alkyl.

-34-

As used herein, "diarylamino" refers to $-C(O)NRR'$ in which R and R' are independently selected from aryl, including lower aryl, such as phenyl.

As used herein, "arylalkylamino" refers to $-C(O)NRR'$ in which one of R and R' is aryl, including lower aryl, such as phenyl, and the other of R and R' is alkyl, including lower alkyl.

As used herein, "arylamino" refers to $-C(O)NHR$ in which R is aryl, including lower aryl, such as phenyl.

As used herein, "hydroxycarbonyl" refers to $-COOH$.

As used herein, "alkoxycarbonyl" refers to $-C(O)OR$ in which R is alkyl, including lower alkyl.

As used herein, "aryloxycarbonyl" refers to $-C(O)OR$ in which R is aryl, including lower aryl, such as phenyl.

As used herein, "alkoxy" and "alkylthio" refer to $RO-$ and $RS-$, in which R is alkyl, including lower alkyl.

As used herein, "aryloxy" and "arylthio" refer to $RO-$ and $RS-$, in which R is aryl, including lower aryl, such as phenyl.

As used herein, "alkylene" refers to a straight, branched or cyclic, in certain embodiments straight or branched, divalent aliphatic hydrocarbon group, in one embodiment having from 1 to about 20 carbon atoms, in another embodiment having from 1 to 12 carbons. In a further embodiment alkylene includes lower alkylene. There may be optionally inserted along the alkylene group one or more oxygen, sulphur or substituted or unsubstituted nitrogen atoms, where the nitrogen substituent is alkyl. Alkylene groups include, but are not limited to, methylene ($-CH_2-$), ethylene ($-CH_2CH_2-$), propylene ($-(CH_2)_3-$), methylenedioxy ($-O-CH_2-O-$) and ethylenedioxy ($-O-(CH_2)_2-O-$). The term "lower alkylene" refers to alkylene groups having 1 to 6 carbons. In

-35-

certain embodiments, alkylene groups are lower alkylene, including alkylene of 1 to 3 carbon atoms.

As used herein, "azaalkylene" refers to $-(CRR)_n-NR-(CRR)_m-$, where n and m are each independently an integer from 0 to 4. As used herein,
 5 "oxaalkylene" refers to $-(CRR)_n-O-(CRR)_m-$, where n and m are each independently an integer from 0 to 4. As used herein, "thiaalkylene" refers to $-(CRR)_n-S-(CRR)_m-$, where n and m are each independently an integer from 0 to 4.

As used herein, "alkenylene" refers to a straight, branched or
 10 cyclic, in one embodiment straight or branched, divalent aliphatic hydrocarbon group, in certain embodiments having from 2 to about 20 carbon atoms and at least one double bond, in other embodiments 1 to 12 carbons. In further embodiments, alkenylene groups include lower alkenylene. There may be optionally inserted along the alkenylene group
 15 one or more oxygen, sulphur or substituted or unsubstituted nitrogen atoms, where the nitrogen substituent is alkyl. Alkenylene groups include, but are not limited to, $-CH=CH-CH=CH-$ and $-CH=CH-CH_2-$. The term "lower alkenylene" refers to alkenylene groups having 2 to 6 carbons. In certain embodiments, alkenylene groups are lower
 20 alkenylene, including alkenylene of 3 to 4 carbon atoms. As used herein, "1,3-diaza-1,3-butadienylene" refers to $-N=CH-N=CH-$. As used herein, "1,2-diaza-1,3-butadienylene" refers to $-N=N-CH=CH-$. As used herein, "2,3-diaza-1,3-butadienylene" refers to $-CH=N-N=CH-$.

As used herein, "azaalkenylene" refers to $-NR-(CR=CR)_n-$, where n
 25 is 1 or 2; and also refers to $-CR=CR-NR-CR=CR-$. As used herein, "oxaalkenylene" refers to $-O-(CR=CR)_n-$, where n is 1 or 2; and also refers to $-CR=CR-O-CR=CR-$. As used herein, "thiaalkenylene" refers to $-S-(CR=CR)_n-$, where n is 1 or 2; and also refers to $-CR=CR-S-CR=CR-$.

-36-

As used herein, "alkynylene" refers to a straight, branched or cyclic, in certain embodiments straight or branched, divalent aliphatic hydrocarbon group, in one embodiment having from 2 to about 20 carbon atoms and at least one triple bond, in another embodiment 1 to 12 carbons. In a further embodiment, alkynylene includes lower alkynylene. There may be optionally inserted along the alkynylene group one or more oxygen, sulphur or substituted or unsubstituted nitrogen atoms, where the nitrogen substituent is alkyl. Alkynylene groups include, but are not limited to, $-\text{C}\equiv\text{C}-\text{C}\equiv\text{C}-$, $-\text{C}\equiv\text{C}-$ and $-\text{C}\equiv\text{C}-\text{CH}_2-$.

10 The term "lower alkynylene" refers to alkynylene groups having 2 to 6 carbons. In certain embodiments, alkynylene groups are lower alkynylene, including alkynylene of 3 to 4 carbon atoms.

As used herein, "alk(en)(yn)ylene" refers to a straight, branched or cyclic, in certain embodiments straight or branched, divalent aliphatic hydrocarbon group, in one embodiment having from 2 to about 20 carbon atoms and at least one triple bond, and at least one double bond; in another embodiment 1 to 12 carbons. In further embodiments, alk(en)(yn)ylene includes lower alk(en)(yn)ylene. There may be optionally inserted along the alkynylene group one or more oxygen, sulphur or substituted or unsubstituted nitrogen atoms, where the nitrogen substituent is alkyl. Alk(en)(yn)ylene groups include, but are not limited to, $-\text{C}=\text{C}-(\text{CH}_2)_n-\text{C}\equiv\text{C}-$, where n is 1 or 2. The term "lower alk(en)(yn)ylene" refers to alk(en)(yn)ylene groups having up to 6 carbons. In certain embodiments, alk(en)(yn)ylene groups have about 4 carbon atoms.

15
20
25

As used herein, "cycloalkylene" refers to a divalent saturated mono- or multicyclic ring system, in certain embodiments of 3 to 10 carbon atoms, in other embodiments 3 to 6 carbon atoms; cycloalkenylene and cycloalkynylene refer to divalent mono- or multicyclic ring

-37-

systems that respectively include at least one double bond and at least one triple bond. Cycloalkenylene and cycloalkynylene groups may, in certain embodiments, contain 3 to 10 carbon atoms, with cycloalkenylene groups in certain embodiments containing 4 to 7 carbon atoms and cycloalkynylene groups in certain embodiments containing 8 to 10 carbon atoms. The ring systems of the cycloalkylene, cycloalkenylene and cycloalkynylene groups may be composed of one ring or two or more rings which may be joined together in a fused, bridged or spiro-connected fashion. "Cycloalk(en)(yn)ylene" refers to a cycloalkylene group containing at least one double bond and at least one triple bond.

As used herein, "substituted alkylene," "substituted alkenylene," "substituted alkynylene," "substituted cycloalkylene," "substituted cycloalkenylene," and "substituted cycloalkynylene" refer to alkylene, alkenylene, alkynylene, cycloalkylene, cycloalkenylene and cycloalkynylene groups, respectively, that are substituted with one or more substituents, in certain embodiments one to three substituents.

As used herein, "arylene" refers to a monocyclic or polycyclic, in certain embodiments monocyclic, divalent aromatic group, in one embodiment having from 5 to about 20 carbon atoms and at least one aromatic ring, in another embodiment 5 to 12 carbons. In further embodiments, arylene includes lower arylene. Arylene groups include, but are not limited to, 1,2-, 1,3- and 1,4-phenylene. The term "lower arylene" refers to arylene groups having 5 or 6 carbons.

As used herein, "heteroarylene" refers to a divalent monocyclic or multicyclic aromatic ring system, in one embodiment of about 5 to about 15 members where one or more, in certain embodiments 1 to 3, of the atoms in the ring system is a heteroatom, that is, an element other than carbon, including but not limited to, nitrogen, oxygen or sulfur.

-38-

As used herein, "heterocyclylene" refers to a divalent monocyclic or multicyclic non-aromatic ring system, in certain embodiments of 3 to 10 members, in one embodiment 4 to 7 members, in another embodiment 5 to 6 members, where one or more, including 1 to 3, of the atoms in the ring system is a heteroatom, that is, an element other than carbon, including but not limited to, nitrogen, oxygen or sulfur.

As used herein, "substituted arylene," "substituted heteroarylene" and "substituted heterocyclylene" refer to arylene, heteroarylene and heterocyclylene groups, respectively, that are substituted with one or more substituents, in certain embodiments one to three substituents.

As used herein, "alkylidene" refers to a divalent group, such as $=CR'R''$, which is attached to one atom of another group, forming a double bond. Alkylidene groups include, but are not limited to, methyldene ($=CH_2$) and ethylidene ($=CHCH_3$). As used herein, "aryalkylidene" refers to an alkylidene group in which either R' or R'' is an aryl group. "Cycloalkylidene" groups are those where R' and R'' are linked to form a carbocyclic ring. "Heterocyclidene" groups are those where at least one of R' and R'' contain a heteroatom in the chain, and R' and R'' are linked to form a heterocyclic ring.

As used herein, "amido" refers to the divalent group $-C(O)NH-$. "Thioamido" refers to the divalent group $-C(S)NH-$. "Oxyamido" refers to the divalent group $-OC(O)NH-$. "Thiaamido" refers to the divalent group $-SC(O)NH-$. "Dithiaamido" refers to the divalent group $-SC(S)NH-$. "Ureido" refers to the divalent group $-HNC(O)NH-$. "Thioureido" refers to the divalent group $-HNC(S)NH-$.

As used herein, "semicarbazide" refers to $-NHC(O)NHNH-$.

"Carbazate" refers to the divalent group $-OC(O)NHNH-$.

"Isothiocarbazate" refers to the divalent group $-SC(O)NHNH-$.

"Thiocarbazate" refers to the divalent group $-OC(S)NHNH-$.

-39-

"Sulfonylhydrazide" refers to the group $-\text{SO}_2\text{NHNH}-$. "Hydrazide" refers to the divalent group $-\text{C}(\text{O})\text{NHNH}-$. "Azo" refers to the divalent group $-\text{N}=\text{N}-$. "Hydrazinyl" refers to the divalent group $-\text{NH}-\text{NH}-$.

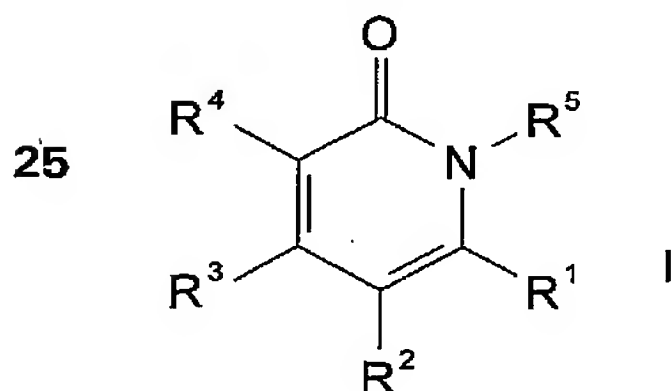
Where the number of any given substituent is not specified (*e.g.*, "haloalkyl"), there may be one or more substituents present. For example, "haloalkyl" may include one or more of the same or different halogens. As another example, " C_{1-3} alkoxyphenyl" may include one or more of the same or different alkoxy groups containing one, two or three carbons.

As used herein, the abbreviations for any protective groups, amino acids and other compounds, are, unless indicated otherwise, in accord with their common usage, recognized abbreviations, or the IUPAC-IUB Commission on Biochemical Nomenclature (see, (1972) *Biochem.* 11:942-944).

B. Heterocyclic Modulators of Nuclear Receptors

Compounds for use in compositions and methods for modulating the activity of nuclear receptors are provided. In particular, compounds for use in compositions and methods for modulating liver X receptors ($\text{LXR}\alpha$ and $\text{LXR}\beta$), either selectively or in combination, and/or orphan nuclear receptors are provided.

In one embodiment, the compounds have formula I:



where, R^2 is substituted or unsubstituted alkyl or hydrogen, where the substituents are selected from one or more Q^1 ; and R^1 , R^3 , R^4 and R^5 are

-40-

selected above. In another embodiment, R^2 is lower alkyl or hydrogen. In another embodiment, R^2 is hydrogen.

In another embodiment, R^1 is selected from substituted or unsubstituted alkyl, substituted or unsubstituted aryl, substituted or
5 unsubstituted heteroaryl, substituted or unsubstituted aralkyl, substituted or unsubstituted heteroaralkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted cycloalkenyl and substituted or unsubstituted heterocyclyl, where the substituents are selected from one or more Q^1 .

10 In another embodiment, R^1 is substituted or unsubstituted aryl, where the substituents are selected from one or more Q^1 .

In another embodiment, R^1 is substituted or unsubstituted heteroaryl, where the substituents are selected from one or more Q^1 .

In another embodiment, R^1 is substituted or unsubstituted
15 heterocyclyl, where the substituents are selected from one or more Q^1 .

In other embodiments, R^1 is substituted or unsubstituted methyl, substituted or unsubstituted cyclohexyl, substituted or unsubstituted cyclopentenyl, substituted or unsubstituted phenyl, substituted or unsubstituted benzyl, substituted or unsubstituted naphthyl, substituted
20 or unsubstituted furyl, substituted or unsubstituted thienyl, substituted or unsubstituted pyrrolyl, substituted or unsubstituted pyrazolyl, substituted or unsubstituted thiazolyl, substituted or unsubstituted piperidinyl, substituted or unsubstituted pyridinyl, substituted or unsubstituted pyrazinyl, substituted or unsubstituted indanyl, substituted or
25 unsubstituted benzofuryl, substituted or unsubstituted thianaphthyl or substituted or unsubstituted indolyl, where the substituents are selected from one or more Q^1 .

In other embodiments, R^1 is substituted or unsubstituted phenyl, substituted or unsubstituted naphthyl, substituted or unsubstituted furyl,

-41-

substituted or unsubstituted thienyl, or substituted or unsubstituted pyrrolyl, where the substituents are selected from one or more Q¹.

In another embodiment, R¹ is substituted or unsubstituted phenyl, substituted or unsubstituted naphthyl, or substituted or unsubstituted thienyl, where the substituents are selected from one or more Q¹.

In other embodiments, R¹ is substituted or unsubstituted furyl, substituted or unsubstituted thienyl, substituted or unsubstituted pyrrolyl, substituted or unsubstituted pyrazolyl, substituted or unsubstituted thiazolyl, substituted or unsubstituted piperidinyl, substituted or unsubstituted pyridinyl, substituted or unsubstituted pyrazinyl, substituted or unsubstituted benzofuryl, substituted or unsubstituted thianaphthyl or substituted or unsubstituted indolyl, where the substituents are selected from one or more Q¹.

In another embodiment, R¹ is substituted or unsubstituted phenyl.

In another embodiment, R¹ is substituted or unsubstituted thienyl.

In certain embodiments, R¹ is unsubstituted or substituted with one or more Q¹, in one embodiment, one to three or five substituents, in another embodiment, one or two substituents, each independently selected from Q¹, where Q¹ is halo, pseudohalo, nitro, hydroxy, amino, hydroxyalkyl, hydroxyalkylaryloxy, hydroxyaryl, hydroxyalkylaryl, hydroxycarbonyl, haloalkyl, alkyl, heterocyclyl, heterocyclylalkyl, aryl, heteroaryl, aralkyl, heteroaralkyl, alkylaralkyl, alkylarylcarbonyl, heterocyclylcarbonyl, alkoxycarbonyl, alkoxycarbonylaryloxy, aryloxy, heteroaryloxy, aralkoxy, alkylaryloxy, alkylaryloxyalkyl, alkylaryloxy, aryloxyalkoxy, aralkoxyaryloxy, alkylarylcycloalkyloxy, alkylheteroaryloxy, cycloalkyloxy, heterocyclylalkoxy, heterocyclyoxy, haloaryloxy, alkylcarbonylaryloxy, arylamino, alkylarylamino, aralkylamino, alkylcarbonylamino, alkylaminocarbonyl,

-42-

haloalkylcarbonylamino and arylthio; and each Q^1 is unsubstituted or further substituted with Q^2 , which is hydrogen, alkyl, aryl, alkoxy, hydroxycarbonyl, alkoxycarbonyl, pseudohalide, halo, aryloxy, aralkoxy, haloalkyl, alkylthio, alkylamino, dialkylamino or hydroxy.

- 5 In another embodiment, R^1 is substituted with Q^1 , which is selected from alkoxycarbonylaryloxy, aryloxy, alkylaryloxy, alkylaryloxyalkyl, alkyl diaryloxy, aryloxyalkoxy, aralkoxyaryloxy, alkylarylcyloalkyloxy, alkylheteroaryloxy, cycloalkyloxy, heterocyclylalkoxy, heterocyclyloxy, heteroaryloxy, haloaryloxy,
- 10 alkoxycarbonylheterocycloxy, alkylcarbonylaryloxy, dialkylaminoaryloxy, alkoxyaryloxy, cyanoaryloxy, aryloxyaryloxy, dialkylaryloxy, haloalkylaryloxy, alkylthioaryloxy, alkylaryl amino, hydroxyaryloxy, arylamino, alkylamino, aralkylamino and arylthio.

- In another embodiment, R^1 is substituted with Q^1 , which is
- 15 selected from alkyl, alkoxy, halo, pseudohalo, haloalkyl, nitro, hydroxy, alkoxy, aralkoxy, heterocyclylalkoxy, alkylcarbonylamino and alkylamino-carbonylamino.

- In another embodiment, R^1 is substituted with Q^1 , which is selected from methyl, ethyl, trifluoromethyl, nitro, hydroxy, n-butyloxy,
- 20 3-(2-piperidinyl)ethoxy, methylcarbonylamino, ethylaminocarbonylamino, chloro, bromo, benzylamino, methylphenoxymethyl, trifluoromethylcarbonylamino, methoxycarbonyl, phenoxy, cyano, n-butoxy, benzoxy, 1-piperidinyl, methoxy, hydroxycarbonyl, tert-butoxycarbonylpiperazinylcarbonyl, hydroxymethyl, 1-piperidinylcarbonyl,
- 25 phenyl, methylphenyl, dimethylamino, methylcarbonylamino, methoxyphenoxy, methylphenoxy, piperidinylmethyl, biphenoxy, benzoxy carbonyl, piperazinylcarbonyl, benzyl, phenylthio, chlorophenoxy, methylbenzyl, hydroxymethylphenoxy, ethoxycarbonylphenoxy, tertbutylmethylphenoxy, tertbutylbiphenoxy, ethylphenoxy,

-43-

isopropylphenoxy, tertbutylphenoxy, N,N-dimethylphenoxy, N,N-phenylmethylamino, 3-methylphenyl-1-amino, trifluoromethylphenoxy, ethylphenoxy, methylcarbonylphenoxy, tetrahydropyranyloxy, tetrahydronaphthoxy, hydroxycarbonylphenoxy, 1,3-hexafluoro-2-

5 hydroxypropylphenylamino, benzoxyphenoxy, cyclohexyloxy, alkylindanyloxy, methoxycarbonylphenoxy, isopropylphenoxy, tert-butylphenoxy, N,N-dimethylaminophenoxy, methoxyphenoxy, methoxycarbonylphenoxy, cyanophenoxy, fluorophenoxy, benzoxyphenoxy, trifluoromethylphenoxy, bromophenoxy, 3,5-

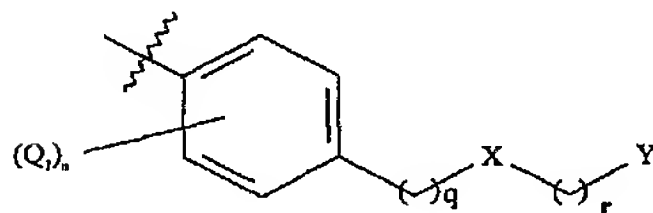
10 ditrifluoromethylphenoxy, methylthiophenoxy, indolyl, tert-butoxycarbonyl-piperidinyloxy, hydroxyphenoxy, pyrimidinoxy and pyrazinoxy.

In another embodiment, R¹ is substituted with Q¹, which is selected from methyl, methoxy, chloro, ethyl, trifluoromethyl, nitro,

15 hydroxy, n-butoxy, 3-(2-piperidinyl)ethoxy, methylcarbonylamino or ethylaminocarbonylamino.

In another embodiment, R¹ has formula IA:

20



25

where, n is an integer from 0 to 4, in one embodiment, from 0 to 2, in another embodiment, 0 or 1; q and r are each independently selected from 0 to 5, in one embodiment 0 to 3,

30 in another embodiment 0 or 1; X is O, S or NR', where R' is alkyl, aryl or hydrogen; Y is substituted or unsubstituted alkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted heterocyclyl or substituted or unsubstituted cycloalkyl,

-44-

where the substituents, when present are selected from one or more Q¹ as above. In another embodiment, Q¹ is selected from halo, hydroxy, alkyl, alkoxy, alkoxycarbonyl, haloalkyl, alkylcarbonyl, hydroxycarbonyl, hydroxyhaloalkyl, aryl, aralkoxy and heteroaryl. In another embodiment, X is O. In another embodiment X is S. In another embodiment, X is NR'. In another embodiment, R' is lower alkyl or hydrogen. In another embodiment, R' is hydrogen. In another embodiment, Y is substituted or unsubstituted aryl. In another embodiment, Y is substituted or unsubstituted heteroaryl. In another embodiment, Y is substituted or unsubstituted phenyl.

In another embodiment, R¹ is methyl, cyclohexyl, 1-cyclopentenyl, 5-indanyl, phenyl, 1-naphthyl, 2-naphthyl, 3-methylphenyl, 2-chlorophenyl, 4-chlorophenyl, 3-ethylphenyl, 3-trifluoromethylphenyl, 3-nitrophenyl, 3-hydroxyphenyl, 3-n-butoxyphenyl, 3-benzyloxyphenyl, 3-(2-piperidinyl)ethoxyphenyl, 3-methylcarbonylaminophenyl, 3-ethylaminocarbonylaminophenyl, 2-methylphenyl, 2-methoxyphenyl, 4-methylphenyl, 3-methoxyphenyl, 4-methoxyphenyl, 3-chlorophenyl, 4-chlorophenyl, 3-benzylaminophenyl, 3-(3-methyl)phenoxyethylphenyl, benzyl, 3-trifluoromethylcarbonylaminophenyl, 3,5-dimethylphenyl, 2-chloro-3-methylphenyl, phenylethyl, 4-butoxyphenyl, 4-methoxycarbonylphenyl, 4-phenoxyphenyl, 4-cyanophenyl, 4-benzoylphenyl, 4-(1-piperidinyl)phenyl, 4-hydroxycarbonylphenyl, 4-(4-tert-butoxycarbonylpiperazin-1-ylcarbonyl)phenyl, 4-hydroxymethylphenyl, 4-(1-piperidinylcarbonyl)phenyl, 4-dimethylaminophenyl, 4-methylcarbonylaminophenyl, 4-nitrophenyl, 6-(1,2,3,4-tetrahydro)naphthyl, 4-(4-methoxyphenoxy)phenyl, 4-(2-methylphenoxy)phenyl, 4-(3-methylphenoxy)phenyl, 4-(4-methylphenoxy)phenyl, 4-(3-methoxyphenoxy)phenyl, 4-(1-piperidinylmethyl)phenyl, 4-(4-biphenoxy)phenyl, 3-(1-benzoxycarbonyl)-

- piperidiny], 4-(1-piperazinylcarbonyl)phenyl, 5-(2-methyl-2,3-dihydro)benzofuryl, 4-benzylphenyl, 4-phenylthiophenyl, 4-(4-chlorophenoxy)-2-chlorophenyl, 4-(3-biphenoxy)phenyl, 4-(1-benzoxycarbonyl)-piperidiny], 4-piperidiny], 4-(1-(3-methylbenzyl))-
- 5 piperidiny], 4-(3-methyl-4-hydroxyphen-1-oxy)phenyl, 4-(2-methyl-4-hydroxyphenoxy)phenyl, 4-(4-ethoxycarbonylphenoxy)phenyl, 4-(2-methyl-4-tertbutylphenoxy)phenyl, 4-(2-phenyl-4-tertbutylphenoxy)phenyl, 4-(3-ethylphenoxy)phenyl, 4-(3-isopropylphenoxy)phenyl, 4-(3-tertbutylphenoxy)phenyl, 4-(3,5-
- 10 dimethylphenoxy)phenyl, 4-phenoxy-2-methylphenyl, 4-(2-methylphenoxy)-2-methylphenyl, 4-(2-methylphenoxy)-3-methylphenyl, 4-N-methyl-N-phenylaminophenyl, 4-(3-trifluoromethylphenoxy)phenyl, 4-(4-ethylphenoxy)phenyl, 4-(4-isopropylphenoxy)phenyl, 4-(4-tertbutylphenoxy)phenyl, 4-(3-methylcarbonylphenoxy)phenyl, 4-(3,4-
- 15 dimethylphenoxy)phenyl, 4-(2-tetrahydropyranyloxy)phenyl, 4-(2-tetrahydropyranyloxy)-3-methylphenyl, 4-hydroxyphenyl, 3-methyl-4-hydroxyphenyl, 4-(4-methylphenoxy)-3-methylphenyl, 4-(2-ethylphenoxy)phenyl, 4-(2-isopropylphenoxy)phenyl, 4-(5,6,7,8-tetrahydronaphthyloxy)phenyl, 4-(3-hydroxycarbonylphenoxy)phenyl, 2-
- 20 methyl-4-hydroxyphenyl, 4-phenoxy-2-hydroxyphenyl, 3-phenoxyphenyl, 4-(4-(1,3-hexafluoro-2-hydroxypropyl)phenylamino)phenyl, 4-(2,3,4-trimethylphenoxy)phenyl, 4-(4-benzyloxyphenoxy)phenyl, 4-(3-(methyl-3-indanyloxy)phenyl, 4-(2-methyl-5-benzothiazoloxy)phenyl, 4-cyclohexyloxyphenyl, 4-(3-methoxycarbonylphenoxy)phenyl, 4-(3-
- 25 isopropylphenoxy)-3-methylphenyl, 4-tert-butyl-phenoxy-3-methylphenyl, 4-N,N-dimethylaminophenoxy-3-methylphenyl, 4-methoxy-phenoxy-3-methylphenyl, 3-methoxy-phenoxy-3-methylphenyl, 4-(3-methoxycarbonyl-phenoxy)-3-methylphenyl, 4-(3-cyanophenoxy)-3-methylphenyl, 4-(4-fluorophenoxy)-3-methylphenyl, 4-(4-benzoxo-

-46-

phenoxy)-3-methylphenyl, 4-(3-benzoxo-phenoxy)-3-methylphenyl, 4-(2,5-dimethylphenoxy)-3-methylphenyl, 4-(2-chlorophenoxy)-3-methylphenyl, 4-(3-chlorophenoxy)-3-methylphenyl, 4-(2-trifluoromethylphenoxy)-3-methylphenyl, 4-(3-trifluoromethylphenoxy)-2-methylphenyl, 4-(3-bromophenoxy)-phenyl, 4-(4-bromophenoxy)-phenyl, 4-(3-benzyloxy-phenoxy)-phenyl, 4-(3-cyanophenoxy)-phenyl, 4-(4-cyanophenoxy)phenyl, 4-(2,4-dimethylphenoxy)-phenyl, 4-(3,5-trifluoromethylphenoxy)phenyl, 4-(4-methylthio-phenoxy)-phenyl, 4-(4-N,N-dimethylamino-phenoxy)-phenyl, 5-indolyloxyphenyl, 4-(1-tert-butoxycarbonyl-piperidin-4-oxy)-phenyl, 4-(4-hydroxyphenoxy)-phenyl, 4-(2-pyrimidinoxy)-phenyl, 4-(2-pyrazinoxy)-phenyl, 2-thienyl, 2-(5-chloro)thienyl, 2-(5-bromo)thienyl, 2-(5-phenyl)thienyl, 3-thianaphthyl, 3-methyl-2-thianaphthyl, 2-(5-(3-methylphenyl))-thienyl, 3-pyridinyl, 2-pyrazinyl, 4-(1-phenyl-5-methyl)pyrazolyl, 2-(1-methyl)pyrrolyl, 3-(1-methyl)indolyl, 3-(1-benzyloxycarbonyl)-piperidinyl, 4-(1-benzyloxyarbonyl)-piperidinyl, 4-piperidinyl, 4-(1-(3-methylbenzyl)-piperidinyl, 2-furyl, 2-(5-methyl)-furyl, 3-(2,5-dimethyl)-furyl, benzofuryl, 3-(2,4-dimethyl)-furyl, 2-thiazolyl or 5-(2,4-dimethyl)thiazolyl.

In another embodiment, R¹ is phenyl, 1-naphthyl, 2-naphthyl, 3-methylphenyl, 3-methoxyphenyl, 2-chlorophenyl, 3-ethylphenyl, 3-trifluoromethylphenyl, 3-nitrophenyl, 3-hydroxyphenyl, 3-n-butoxyphenyl, 3-benzyloxyphenyl, 3-(2-piperidinyl)ethoxyphenyl, 3-methylcarbonylaminophenyl, 3-ethylaminocarbonylaminophenyl, 2-methylphenyl, 2-methoxyphenyl, 4-methylphenyl, 3-methoxyphenyl, 4-methoxyphenyl, 3-chlorophenyl or 4-chlorophenyl.

In another embodiment, R¹ is 3-(3-methyl)phenoxy-methylphenyl, 4-phenoxyphenyl, 4-benzoxo-phenyl, 4-(4-methoxyphenoxy)phenyl, 4-(2-methylphenoxy)phenyl, 4-(3-methylphenoxy)phenyl, 4-(4-methylphenoxy)phenyl, 4-(3-methoxyphenoxy)phenyl, 4-(4-

-47-

- biphenoxy)phenyl, 4-(4-chlorophenoxy)-2-chlorophenyl, 4-(3-biphenoxy)phenyl, 4-(3-methyl-4-hydroxyphenoxy)phenyl, 4-(2-methyl-4-hydroxyphenoxy)phenyl, 4-(4-ethoxycarbonylphenoxy)phenyl, 4-(2-methyl-4-tertbutylphenoxy)phenyl, 4-(2-phenyl-4-tertbutylphenoxy)phenyl, 4-(3-ethylphenoxy)phenyl, 4-(3-isopropylphenoxy)phenyl, 4-(3-tertbutylphenoxy)phenyl, 4-(3,5-dimethylphenoxy)phenyl, 4-phenoxy-2-methylphenyl, 4-(2-methylphenoxy)-2-methylphenyl, 4-(2-methylphenoxy)-3-methylphenyl, 4-(3-trifluoromethylphenoxy)phenyl, 4-(4-ethylphenoxy)phenyl, 4-(4-isopropylphenoxy)phenyl, 4-(4-tertbutylphenoxy)phenyl, 4-(3-methylcarbonylphenoxy)phenyl, 4-(3,4-dimethylphenoxy)phenyl, 4-(4-methylphenoxy)-3-methylphenyl, 4-(2-ethylphenoxy)phenyl, 4-(2-isopropylphenoxy)phenyl, 4-(5,6,7,8-tetrahydronaphthyloxy)phenyl, 4-(3-hydroxycarbonylphenoxy)phenyl, 2-methyl-4-hydroxyphenyl, 4-phenoxy-2-hydroxyphenyl, 3-phenoxyphenyl, 4-(2,3,4-trimethylphenoxy)phenyl, 4-(4-benzyloxyphenoxy)phenyl, 4-(3-methoxycarbonylphenoxy)phenyl, 4-(3-isopropylphenoxy)-3-methylphenyl, 4-tert-butyl-phenoxy-3-methylphenyl, 4-N,N-dimethylaminophenoxy-3-methylphenyl, 4-methoxy-phenoxy-3-methylphenyl, 3-methoxy-phenoxy-3-methylphenyl, 4-(3-methoxycarbonyl-phenoxy)-3-methylphenyl, 4-(3-cyanophenoxy)-3-methylphenyl, 4-(4-fluorophenoxy)-3-methylphenyl, 4-(4-benzoxy-phenoxy)-3-methylphenyl, 4-(3-benzoxy-phenoxy)-3-methylphenyl, 4-(2,5-dimethylphenoxy)-3-methylphenyl, 4-(2-chlorophenoxy)-3-methylphenyl, 4-(3-chlorophenoxy)-3-methylphenyl, 4-(2-trifluoromethylphenoxy)-3-methylphenyl, 4-(3-trifluoromethylphenoxy)-2-methylphenyl, 4-(3-bromophenoxy)-phenyl, 4-(4-bromophenoxy)-phenyl, 4-(3-benzyloxy-phenoxy)-phenyl, 4-(3-cyanophenoxy)-phenyl, 4-(4-cyanophenoxy)phenyl, 4-(2,4-dimethylphenoxy)-phenyl, 4-(3,5-

-48-

trifluoromethylphenoxy)phenyl, 4-(4-methylthio-phenoxy)-phenyl or 4-(4-N,N-dimethylamino-phenoxy)-phenyl.

In another embodiment, R¹ is 4-N-methyl-N-phenylaminophenyl, 4-(4-(1,3-hexafluoro-2-hydroxypropyl)phenyl-1-amino)phenyl or 4-

5 phenylthiophenyl.

In another embodiment, R¹ is 2-thienyl, 2-(5-chloro)thienyl, 2-(5-bromo)thienyl, 2-(5-phenyl)thienyl, 3-thianaphthyl, 3-methyl-2-thianaphthyl or 2-(5-(3-methylphenyl))-thienyl. In another embodiment, R¹ is thienyl. In another embodiment, R¹ is 2-thienyl.

10 In another embodiment, R¹ is 3-pyridinyl, 2-pyrazinyl, 4-(1-phenyl-5-methyl)pyrazolyl, 2-(1-methyl)pyrrolyl, 3-(1-methyl)indolyl, 3-(1-benzyloxycarbonyl)-piperidinyl, 4-(1-benzyloxycarbonyl)-piperidinyl, 4-piperidinyl or 4-(1-(3-methylbenzyl)-piperidinyl.

In another embodiment, R¹ is 2-furyl, 2-(5-methyl)-furyl, 3-(2,5-dimethyl)-furyl, benzofuryl or 3-(2,4-dimethyl)-furyl.

15 In another embodiment, R¹ is 2-thiazolyl or 5-(2,4-dimethyl)thiazolyl.

In another embodiment, R³ is substituted or unsubstituted alkyl, substituted or unsubstituted alkylaryl, substituted or unsubstituted aryl, substituted or unsubstituted alkoxycarbonyl or substituted or unsubstituted alkylaminocarbonyl, where the substituents are selected from one or more Q¹. In another embodiment, R³ is substituted or unsubstituted alkyl or substituted or unsubstituted aryl. In another embodiment, R³ is substituted or unsubstituted alkoxycarbonyl. In another embodiment, R³ is substituted or unsubstituted alkyl. In another embodiment, R³ is haloalkyl. In certain embodiments, R³ is substituted with Q¹, which is halo, pseudohalo, alkyl, alkoxy, alkoxycarbonyl or aryloxycarbonyl. In another embodiments, R³ is substituted with Q¹,

-49-

which is halo. In further embodiments, R^3 is substituted with Q^1 , which is fluoro, chloro, phenyl, methyl, methoxy or methylamino.

In further embodiments, R^3 is substituted or unsubstituted methyl, or substituted or unsubstituted phenyl. In another embodiment, R^3 is
5 methyl, trifluoromethyl, pentafluoroethyl, heptafluoropropyl, chlorodifluoromethyl, 1-(1-methoxy-1-fluoro)ethyl, methoxycarbonyl, ethoxycarbonyl, methylaminocarbonyl, dimethoxymethyl, methoxycarbonylmethyl or phenyl. In another embodiment, R^3 is trifluoromethyl, methyl, methoxycarbonylmethyl or phenyl.

10 In another embodiment, R^4 is hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted alkynyl, pseudohalide, hydroxycarbonyl, $CH_2NR^{31}R^{32}$ or NO_2 ; where the substituents are each independently selected from one or more Q^1 . In another embodiment, R^4 is pseudohalide. In another embodiment, R^4 is substituted or
15 unsubstituted methyl, substituted or unsubstituted acetyl. In another embodiment, R^4 is substituted or unsubstituted acetyl, where the substituent is trialkylsilyl. In further embodiments, R^4 is substituted with Q^1 , which is trialkylsilyl, alkylcarbonylamino, arylcarbonylamino, aralkylcarbonylamino, alkoxycarbonylamino, dialkylamino, alkylamino or
20 amino.

In another embodiment, R^4 is alkylcarbonylaminoalkyl, alkoxycarbonylaminoalkyl, aralkoxycarbonylaminoalkyl or aryloxycarbonylaminoalkyl. In another embodiment, R^4 is hydrogen, cyano, nitro, hydroxycarbonyl, trimethylsilylacetyl, acetyl,
25 methylcarbonylaminomethyl, ethylcarbonylaminomethyl, n-propylcarbonylaminomethyl, isopropylcarbonylaminomethyl, n-octylcarbonylaminomethyl, phenylcarbonylaminomethyl, benzylcarbonylaminomethyl, phenylethylcarbonylaminomethyl,

-50-

ethoxycabonylaminomethyl dimethylaminomethyl or aminomethyl. In another embodiment, R^4 is cyano.

In certain embodiments, R^3 and R^4 , together with the atoms to which they are attached, form substituted or unsubstituted heterocyclic ring. In certain embodiments, R^3 and R^4 , together with the atoms to which they are attached, form substituted or unsubstituted heterocyclic ring, with the proviso that the nitrogen atom in the heterocyclic ring is not substituted with a phenyl group. In certain embodiments, R^3 and R^4 , together with the atoms to which they are attached, form substituted or unsubstituted heterocyclic ring, with the proviso that the heterocyclic ring does not have more than one oxo substituent. In another embodiment, R^3 and R^4 together with the atoms to which they are attached form 2-oxotetrahydropyridine or 2-oxo-3-pyrroline.

In another embodiment, R^5 is substituted or unsubstituted alkyl, substituted or unsubstituted aralkyl, substituted or unsubstituted aryl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted heterocyclalkyl, substituted or unsubstituted heteroaryl, substituted or unsubstituted heteroaralkyl, $-N=CR^6R^7$ or $-NR^9R^{10}$. In another embodiment, R^5 is substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted aralkyl, substituted or unsubstituted heteroaralkyl, $-N=CR^6R^7$ or $-NR^9R^{10}$. In another embodiment, R^5 is substituted or unsubstituted aryl, substituted or unsubstituted aralkyl, $-N=CR^6R^7$ or $-NR^9R^{10}$. In further embodiments, R^5 is substituted or unsubstituted aralkyl, or $-N=CR^6R^7$. In another embodiment, R^5 is substituted or unsubstituted aralkyl. In another embodiment, R^5 is substituted or unsubstituted heterocyclalkyl. In another embodiment, R^5 is substituted or unsubstituted heteroaralkyl. In another embodiment, R^5 is $-N=CR^6R^7$. In another embodiment, R^5 is substituted or unsubstituted heterocyclyl.

-51-

In another embodiment, R⁵ is substituted or unsubstituted methyl, substituted or unsubstituted ethyl, substituted or unsubstituted propyl, substituted or unsubstituted phenyl, substituted or unsubstituted piperidiny, substituted or unsubstituted benzyl, substituted or
5 unsubstituted 2-phenethyl, substituted or unsubstituted 1-phenethyl, substituted or unsubstituted 3-phenylpropyl, substituted or unsubstituted 1,2,3,4-tetrahydro-1-naphthyl, substituted or unsubstituted 3-pyridylmethyl, substituted or unsubstituted 4-pyridylmethyl, substituted or unsubstituted 2-pyrazinyl, substituted or unsubstituted thiazolylmethyl,
10 substituted or unsubstituted oxazolylmethyl.

In another embodiment, R⁵ is substituted or unsubstituted phenyl, substituted or unsubstituted benzyl, substituted or unsubstituted 2-phenethyl, substituted or unsubstituted 1-phenethyl, substituted or unsubstituted 3-phenylpropyl, substituted or unsubstituted 1,2,3,4-
15 tetrahydro-1-naphthyl, substituted or unsubstituted 3-pyridylmethyl, substituted or unsubstituted 4-pyridylmethyl, -N=CR⁶R⁷ or -NR⁹R¹⁰.

In another embodiment, R⁵ is substituted or unsubstituted piperidiny, substituted or unsubstituted 3-pyridylmethyl, substituted or unsubstituted 4-pyridylmethyl, substituted or unsubstituted 2-pyrazinyl,
20 substituted or unsubstituted thiazolylmethyl, or substituted or unsubstituted oxazolylmethyl.

In another embodiment, R⁵ is substituted or unsubstituted benzyl.

In certain embodiments, R⁵ is unsubstituted or substituted with one or more, in one embodiment, one, two or three Q¹ groups, where Q¹
25 is alkyl, haloalkyl, halohydroxyalkyl, alkoxy, alkoxyalkoxyalkyl, alkoxyalkyl, aryl, halo, alkoxycarbonyl, alkylthio, aryloxy, haloalkoxy, aralkyl, heteroaryl, hydroxy, hydroxyalkyl, heterocyclyl, heterocyclylalkyl, alkylcarbonyl, arylcarbonyl, alkylalkelenedioxy or dialkylalkelenedioxy. In other embodiments, R⁵ is unsubstituted or substituted with one or more

-52-

Q¹ groups, where Q¹ is alkyl, haloalkyl, alkoxy, aryl, halo, alkoxy carbonyl, alkylthio, aryloxy, haloalkoxy, aralkyl, heteroaryl, hydroxy, alkyl carbonyl or aryl carbonyl.

In other embodiments, R⁵ is unsubstituted or substituted with one or more, in one embodiment one, two or three, Q¹ groups, where Q¹ is methyl, isopropyl, trifluoromethyl, methoxy, fluoro, bromo, methoxycarbonyl, chloro, methylthio, phenoxy, trifluoromethoxy, 3-pyridyl, 4-pyridyl, 2-pyridyl, ethyl, n-propyl, cyclohexyl, n-propyloxymethyl, n-pentyloxymethyl, n-octyloxymethyl, ethoxymethyl, n-butoxymethyl, n-hexyloxymethyl, n-octyloxymethyl, tert-butyl, ethoxycarbonyl, methyl carbonyl, hydroxy, phenyl, benzyl, n-butyl, ethoxy, phenyl carbonyl, 2-(2-methyl)-methylenedioxy, 1-piperidinyl, 5-(2,2-dimethyl)-methylenedioxy, methoxymethoxymethyl, hydroxymethyl, hydroxyethyl, methoxymethyl, 1-piperidinylmethyl or 1,3-trifluoro-2-hydroxypropyl.

In another embodiment, Q¹ is methyl, trifluoromethyl, methoxy, fluoro, bromo, methoxycarbonyl, chloro, methylthio, phenoxy, trifluoromethoxy, 3-pyridyl, 4-pyridyl, 2-pyridyl, ethyl, tert-butyl, ethoxycarbonyl, methyl carbonyl, hydroxy, phenyl, benzyl, n-butyl, ethoxy or phenyl carbonyl.

In another embodiment, R⁵ is 2,4-dimethylbenzyl, 4-isopropylbenzyl, 4-tert-butylbenzyl, 2,4,5-trifluorobenzyl, 1-naphthylmethyl, 4-(2-(2-methyl)-1,3-dioxymethylene)benzyl, 4-methylbenzyl, 4-ethylbenzyl, 1-piperidinyl, 4-methyl carbonylbenzyl, 5-(2,2-dimethyl)-1,3-dioxymethylenemethyl, 1,2-dihydroxypropyl, benzyl, 4-(2-methyl)-thiazolylmethyl, 4-(2-phenyl)thiazolylmethyl, 3-methoxymethoxymethylbenzyl, 3-hydroxymethylbenzyl, 4-hydroxymethylbenzyl, 4-hydroxyethylbenzyl, 4-methoxymethylbenzyl, 4-(1-piperidinylmethyl)benzyl, 3-biphenyl, 4-biphenyl, 4-(1,3-trifluoro-2-

hydroxypropyl)phenyl, 4-(2-ethyl)thiazolymethyl, 4-(2-isopropyl)thiazolymethyl, 4-(2-propyl)thiazolymethyl, 4-(2-benzyl)thiazolymethyl, 4-(2-methyl)oxazolymethyl, 4-(2-ethyl)oxazolymethyl, 4-(2-propyl)oxazolymethyl, 4-(2-phenyl)oxazolymethyl, 4-(2-benzyl)oxazolymethyl, 4-(2-cyclohexyl)oxazolymethyl, 4-n-propyloxymethylbenzyl, 2-(5-methyl)pyrazinylmethyl, 4-n-pentyloxymethylbenzyl, 4-n-octyloxymethylbenzyl, 3-ethoxymethylbenzyl, 3-n-butoxymethylbenzyl, 3-n-hexyloxymethylbenzyl, 3-n-octyloxymethylbenzyl, 2-methylbenzyl, 4-methylbenzyl, 3-methylbenzyl, phenylethyl, 4-(2,5-dimethyl)thiazolymethyl, 4-(2-isopropyl-5-methyl)thiazolymethyl, 4-(2-ethyl-5-methyl)thiazolymethyl, 4-(2-methyl-5-ethyl)thiazolymethyl, 4-(2,5-diethyl)thiazolymethyl, phenyl, 2-phenylethyl, 3-phenylpropyl, benzyl, 3-methylbenzyl, 2-trifluoromethylbenzyl, 3-trifluoromethylbenzyl, 4-trifluoromethylbenzyl, 2-methoxybenzyl, 3-methoxybenzyl, 4-methoxybenzyl, 4-phenylbenzyl, 1-phenylethyl, 1,2,3,4-tetrahydro-1-naphthyl, 2-fluorobenzyl, 4-fluorobenzyl, 2,4-difluorobenzyl, 4-bromobenzyl, 4-methoxycarbonylbenzyl, 2-chlorobenzyl, 4-chlorobenzyl, 4-methylthiobenzyl, 4-phenoxybenzyl, 4-trifluoromethoxybenzyl, 3-pyridylmethyl or 4-pyridylmethyl.

In another embodiment, R⁵ is 4-(2-(2-methyl)-1,3-dioxymethylene)benzyl, 1-piperidinyl, 5-(2,2-dimethyl)-1,3-dioxymethelenemethyl, 4-(2-methyl)-thiazolymethyl, 4-(2-phenyl)thiazolymethyl, 4-(1-piperidinylmethyl)benzyl, 4-(2-ethyl)thiazolymethyl, 4-(2-isopropyl)thiazolymethyl, 4-(2-propyl)thiazolymethyl, 4-(2-benzyl)thiazolymethyl, 4-(2-methyl)oxazolymethyl, 4-(2-ethyl)oxazolymethyl, 4-(2-propyl)oxazolymethyl, 4-(2-phenyl)oxazolymethyl, 4-(2-benzyl)oxazolymethyl, 4-(2-cyclohexyl)oxazolymethyl, 2-(5-

-54-

methyl)pyrazinylmethyl, 4-(2,5-dimethyl)thiazolylmethyl, 4-(2-isopropyl-5-methyl)thiazolylmethyl, 4-(2-ethyl-5-methyl)thiazolylmethyl, 4-(2-methyl-5-ethyl)thiazolylmethyl, 4-(2,5-diethyl)thiazolylmethyl, 3-pyridylmethyl or 4-pyridylmethyl.

- 5 In another embodiment, R^5 is phenyl, 2-phenylethyl, 3-phenylpropyl, benzyl, 2-methylbenzyl, 3-methylbenzyl, 4-methylbenzyl, 2-trifluoromethylbenzyl, 3-trifluoromethylbenzyl, 4-trifluoromethylbenzyl, 2-methoxybenzyl, 3-methoxybenzyl, 4-methoxybenzyl, 4-phenylbenzyl, 1-phenylethyl, 2,4-dimethylbenzyl, 2-fluorobenzyl, 4-fluorobenzyl, 2,4-
- 10 difluorobenzyl, 4-bromobenzyl, 4-methoxycarbonylbenzyl, 2-chlorobenzyl, 4-chlorobenzyl, 4-methylthiobenzyl, 4-phenoxybenzyl, 4-trifluoromethoxybenzyl, 3-pyridylmethyl, or 4-pyridylmethyl.

- In another embodiment, R^5 is $-N=CR^6R^7$ where R^6 and R^7 are each independently hydrogen, substituted or unsubstituted alkyl, or
- 15 substituted or unsubstituted aryl; or together form substituted or unsubstituted alkylene, substituted or unsubstituted alkenylene, or $-(CH_2)_xX(CH_2)_y-$ where x and y are each 2, and X is O or NR^8 ; where R^8 is substituted or unsubstituted alkyl, substituted or unsubstituted alkylcarbonyl, or substituted or unsubstituted arylcarbonyl.

- 20 In other embodiments, R^6 and R^7 are each independently hydrogen, substituted or unsubstituted methyl, substituted or unsubstituted ethyl, substituted or unsubstituted n-propyl, substituted or unsubstituted i-propyl, substituted or unsubstituted i-butyl, substituted or unsubstituted tert-butyl, substituted or unsubstituted phenyl, substituted or
- 25 unsubstituted s-butyl, substituted or unsubstituted 3-pentyl, or substituted or unsubstituted naphthyl; where the substituents are selected from one or more Q^1 . In another embodiment, R^6 and R^7 are unsubstituted or substituted with one or more, in one embodiment one or two, Q^1 groups, where Q^1 is hydroxy, halo, alkyl or alkoxy. In another

-55-

embodiment, R^6 and R^7 are unsubstituted or substituted with one or more, in one embodiment one or two, Q^1 groups, where Q^1 is hydroxy, chloro, bromo, methyl or methoxy.

In other embodiments, R^6 and R^7 are each independently hydrogen, methyl, phenyl, ethyl, isopropyl, n-propyl, s-butyl, 3-pentyl, isobutyl, t-butyl, 2-naphthyl, 2-hydroxyphenyl, 2-hydroxy-5-chlorophenyl, 4-bromophenyl, 2-hydroxy-4-bromophenyl, 2-methylphenyl or 4-methoxyphenyl. In other embodiments, R^6 and R^7 are each independently hydrogen, methyl, ethyl, isopropyl, n-propyl, s-butyl, 3-pentyl, isobutyl or t-butyl.

In another embodiment, R^6 and R^7 together form substituted or unsubstituted alkylene, substituted or unsubstituted alkenylene, or $-(CH_2)_xX(CH_2)_y-$ where x and y are each 2, and X is O or NR^8 , where the substituents are selected from one or more Q^1 . In other embodiments, R^6 and R^7 together form substituted or unsubstituted butylene, substituted or unsubstituted pentylene, substituted or unsubstituted hexylene, or substituted or unsubstituted pentenylene, where the substituents are selected from one or more Q^1 . In other embodiments, R^6 and R^7 are unsubstituted or substituted with one or more, in one embodiment one or two, substituents selected from Q^1 , which is alkyl, alkoxycarbonyl, aryl, aralkyl, halo, alkoxy and alkylthio. In other embodiments, R^6 and R^7 are unsubstituted or substituted with one or more, in one embodiment one or two, substituents selected from Q^1 , which is methyl, ethyl, tert-butyl, ethoxycarbonyl, ethyl, phenyl, benzyl, n-butyl, chloro, methoxy, ethoxy, methylthio and methoxycarbonyl.

In another embodiment, R^6 and R^7 together form $-(CH_2)_xX(CH_2)_y-$ where x and y are each 2, and X is O or NR^8 , where R^8 is substituted or unsubstituted alkyl, substituted or unsubstituted alkylcarbonyl, or substituted or unsubstituted arylcarbonyl, and the substituents are

-56-

selected from one or more Q^1 . In other embodiments, R^8 is alkyl, alkylcarbonyl or arylcarbonyl. In another embodiment, R^8 is methyl, methylcarbonyl or phenylcarbonyl.

In other embodiments, R^6 and R^7 together form pentylene, 2,2,4,4-tetramethylpentylene, 3,3-dimethyl-1-pentenylene, 2-methyl-1-pentenylene, 3-methylpentylene, 3-ethylpentylene, 3-tert-butylpentylene, 1-methylpentylene, 2-methylpentylene, hexylene, butylene, 1-methylbutylene, 2-methylbutylene, 1,3-ethylenebutylene, 3-ethoxycarbonylpentylene, 1-ethylpentylene, 1-phenylpentylene, 1-benzylpentylene, 1-n-butylpentylene, 1,1-dimethylpentylene, 1-chloropentylene, 1-methoxypentylene, 1-ethoxypentylene, 1-methylthiopentylene or 1-methoxycarbonylpentylene.

In another embodiment, R^5 is $-NR^9R^{10}$, where R^9 and R^{10} are each independently hydrogen, or substituted or unsubstituted aryl. In another embodiment, R^9 and R^{10} are each independently hydrogen, or substituted or unsubstituted phenyl. In another embodiment, R^9 and R^{10} are each independently hydrogen or phenyl.

In another embodiment, the compounds for use in the compositions and methods provided herein have formula I, where R^1 is substituted or unsubstituted aryl, substituted or unsubstituted aralkyl, substituted or unsubstituted heteroaryl, or substituted or unsubstituted heteroaralkyl; R^2 is hydrogen, or substituted or unsubstituted alkyl; R^3 is haloalkyl; R^4 is cyano; and R^5 is substituted or unsubstituted aryl, substituted or unsubstituted aralkyl, substituted or unsubstituted heterocyclyl, or $-N=CR^6R^7$; where R^6 and R^7 are each independently hydrogen or substituted or unsubstituted alkyl;

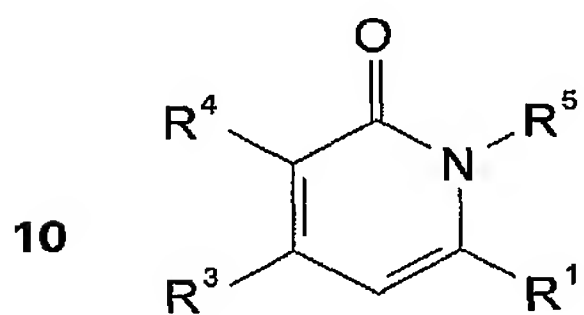
where the alkyl, heterocyclyl, aryl, heteroaryl, aralkyl and heteroaralkyl moieties of R^1 , R^2 , R^3 , R^5 , R^6 and R^7 are unsubstituted or substituted with one or more substituents, in one embodiment one to

-57-

three or four substituents, each independently selected from Q¹, as defined above.

In another embodiment, the compounds for use in the compositions and methods have formula II:

5

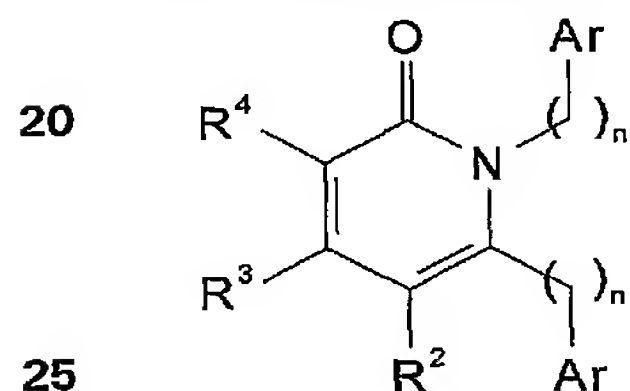


10

15 where R¹, R³, R⁴ and R⁵ are selected as above.

In another embodiment, the compounds for use in the compositions and methods have formula III:

20



25

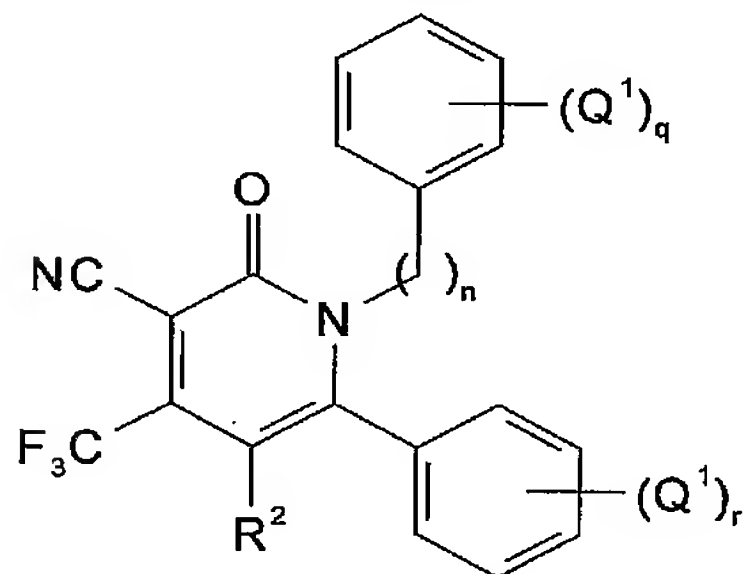
where R², R³ and R⁴ are selected as above; each Ar is independently substituted or unsubstituted aryl, substituted or unsubstituted cycloalkyl; substituted or unsubstituted heteroaryl, or substituted or unsubstituted heterocyclyl, where there are 0 to 5 substituents, in one embodiment 0, 1, 2 or 3 substituents, each independently selected from Q¹; and each n is independently an integer from 0 to 6, in one embodiment 0 to 3, in another embodiment 0 or 1.

35 In another embodiment, the compounds are of formula III where R² is hydrogen. In another embodiment, the compounds have formula III where R³ is haloalkyl. In another embodiment, the compounds have

-58-

formula III where R^3 is perfluoroalkyl. In another embodiment, the compounds have formula III where R^3 is trifluoromethyl or pentafluoroethyl. In another embodiment, the compounds have formula III where R^3 is trifluoromethyl. In another embodiment, the compounds have formula III where R^4 is cyano. In another embodiment, the compounds have formula III where Ar is substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, or substituted or unsubstituted heterocyclyl. In another embodiment, the compounds have formula III where Ar is N-pyrrolidinyl.

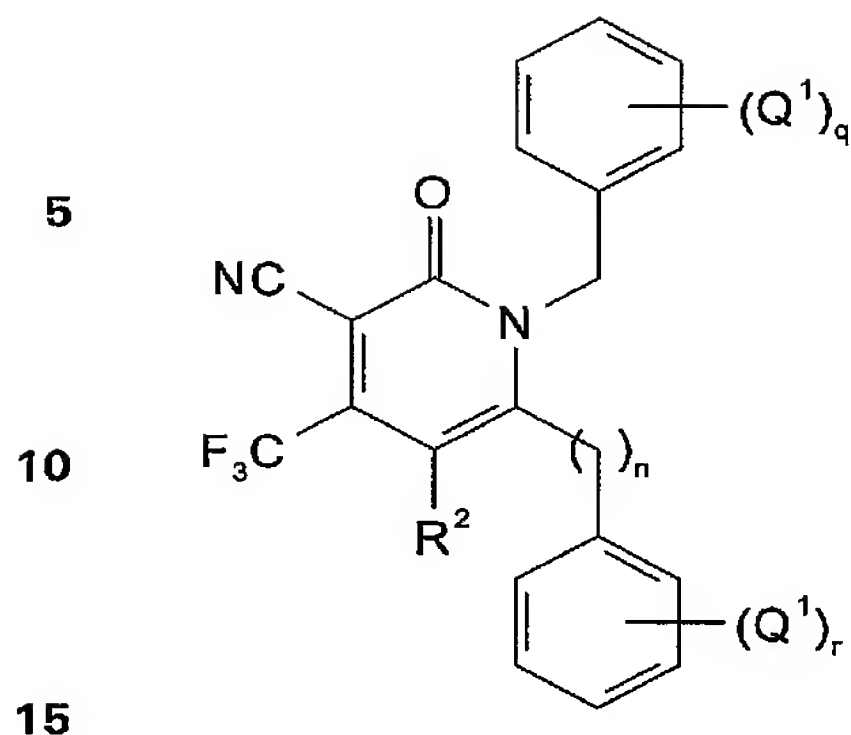
In another embodiment, the compounds for use in the compositions and methods provided herein have formula IV:



where R^2 , Q^1 and n are selected as above; and q and r are each independently an integer from 0 to 5, or from 0 to 3, or 0 or 1.

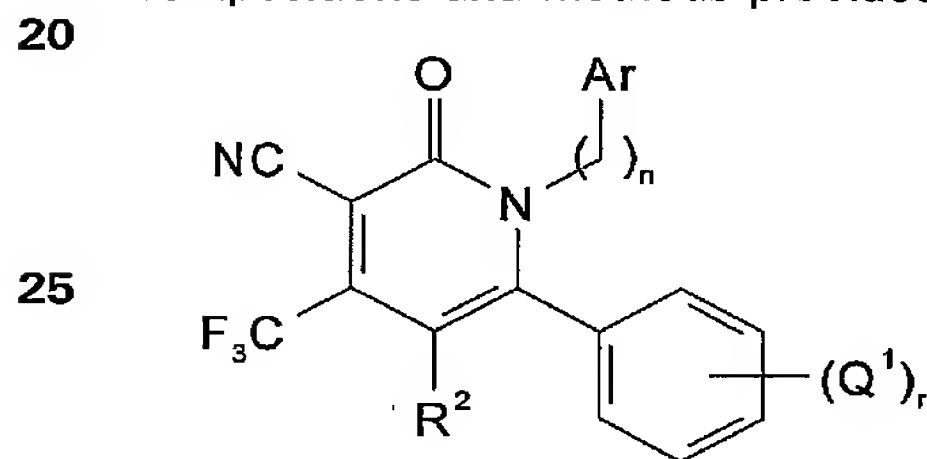
In another embodiment, the compounds for use in the compositions and methods provided herein have formula V:

-59-



where R^2 , Q^1 , q , r and n are selected as above.

In another embodiment, the compounds for use in the compositions and methods provided herein have formula VI:

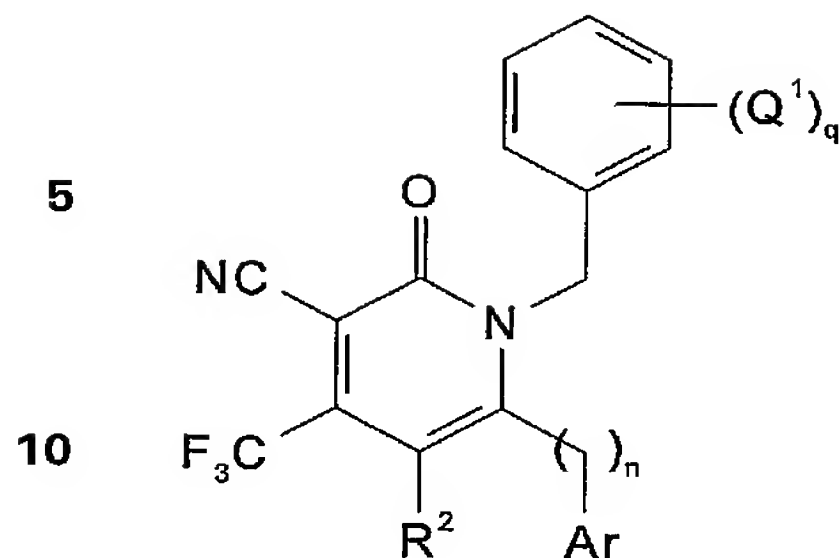


30 where Ar , R^2 , Q^1 , r and n are selected as above. In another embodiment, the compounds have formula VI where Ar is substituted or unsubstituted heteroaryl.

35 In another embodiment, the compounds for use in the compositions and methods provided herein have formula VII:

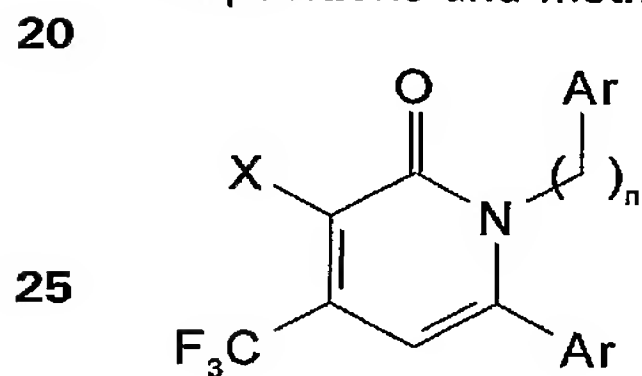
40

-60-



where Ar, R², Q¹, q and n are selected as above.

In another embodiment, the compounds for use in the compositions and methods provided herein have formula VIII:



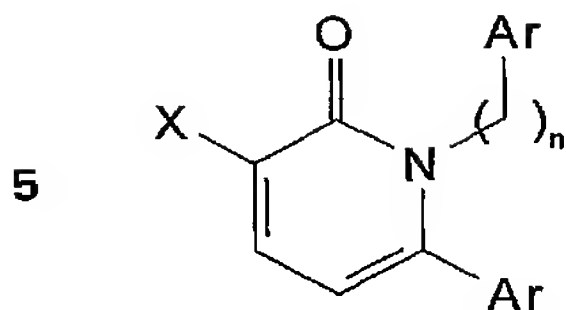
30 where each Ar is independently selected as above; n is selected as above; and X is cyano, nitro or NR³¹R³², where R³¹ and R³² are selected as above.

In another embodiment, the compounds for use in the compositions and methods provided herein have formula IX:

35

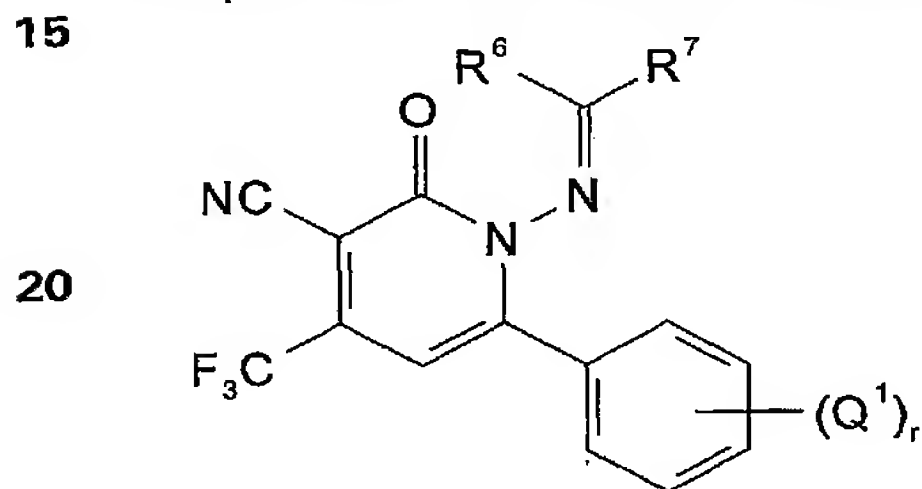
40

-61-



10 where each Ar is independently selected as above; n is selected as above; and X is bromo, CHO, COOR³⁰ or CONR³¹R³², where R³⁰, R³¹ and R³² are selected as above.

In another embodiment, the compounds for use in the compositions and methods provided herein have formula X:



where Q¹, r, R⁶ and R⁷ are selected as above.

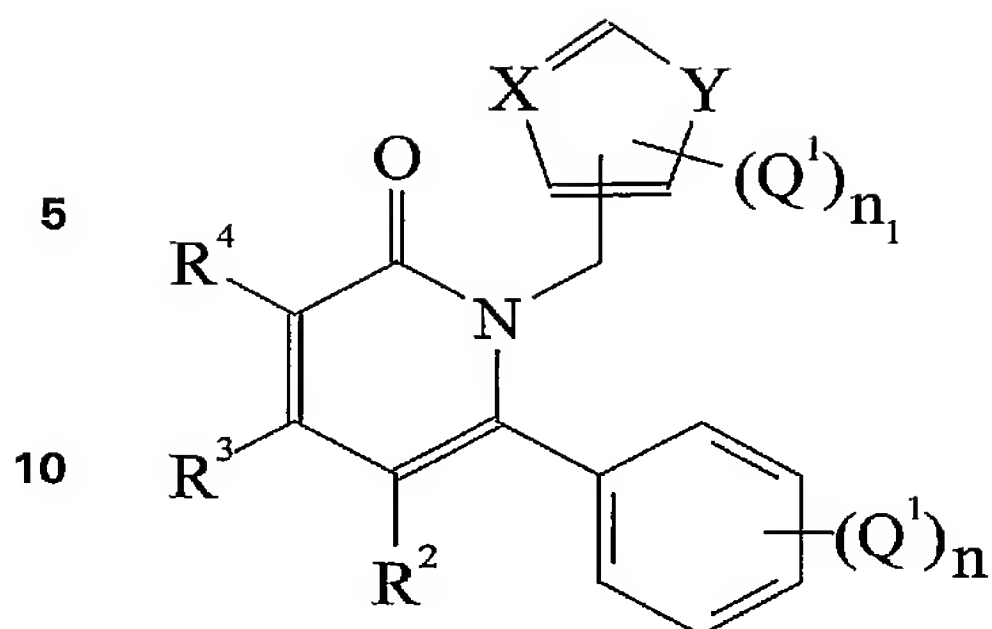
In another embodiment, the compounds for use in the compositions and methods provided herein have formula XI:

30

35

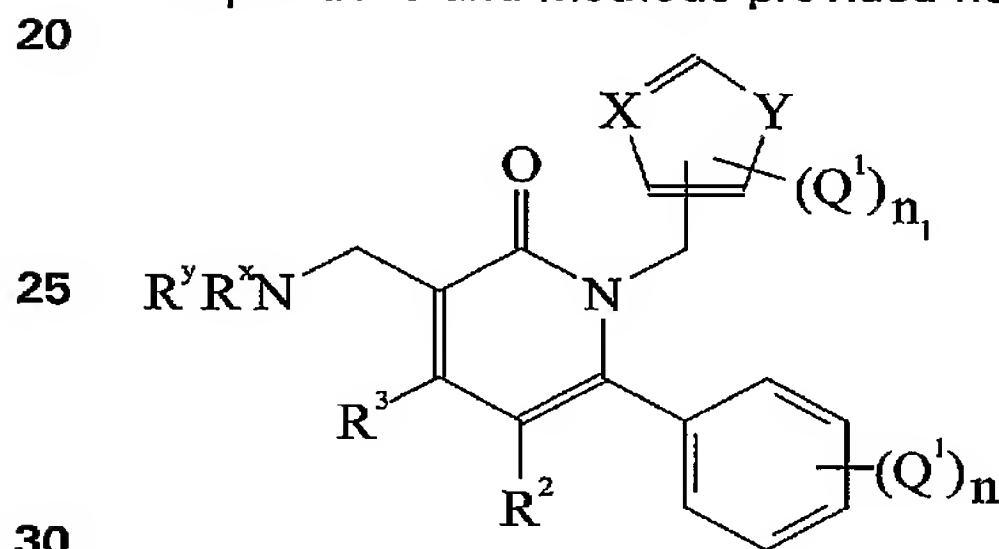
40

-62-



- 15 wherein n is an integer from 0 to 5; n_1 is an integer from 0 to 2; Y is selected from O, S and NR' , where R' is hydrogen, alkyl or aryl; X is N; Q^1 , R^2 , R^3 and R^4 are selected as above.

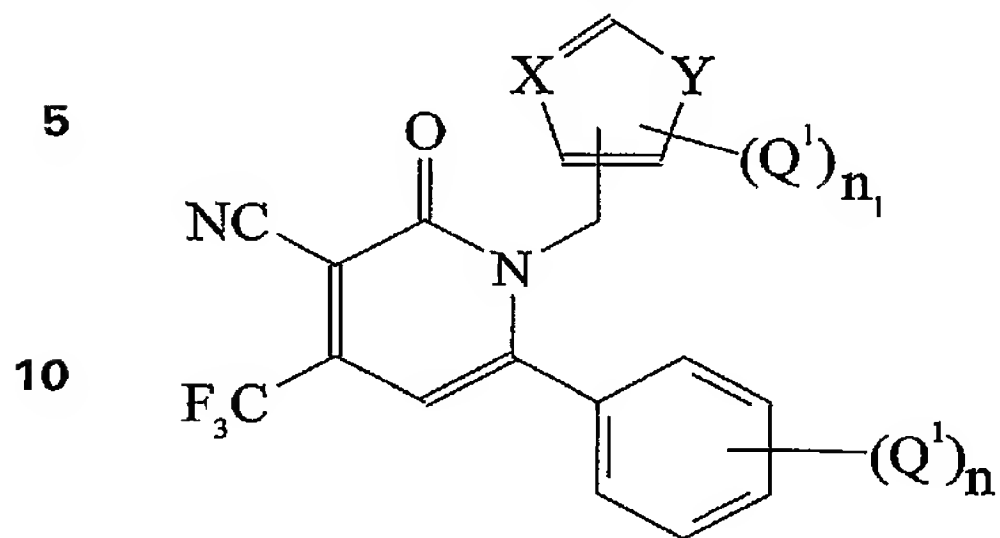
In another embodiment, the compounds for use in the compositions and methods provided herein have formula XII:



- wherein n is an integer from 0 to 5; n_1 is an integer from 0 to 2; Y is selected from O, S and NR' , where R' is hydrogen, alkyl or aryl; X is N; R^x and R^y are each independently selected from hydrogen, alkyl, alkylcarbonyl, aryl, arylcarbonyl, aralkylcarbonyl, alkoxycarbonyl, aryloxycarbonyl and aralkoxycarbonyl; Q^1 , R^2 , R^3 and R^4 are selected as above.

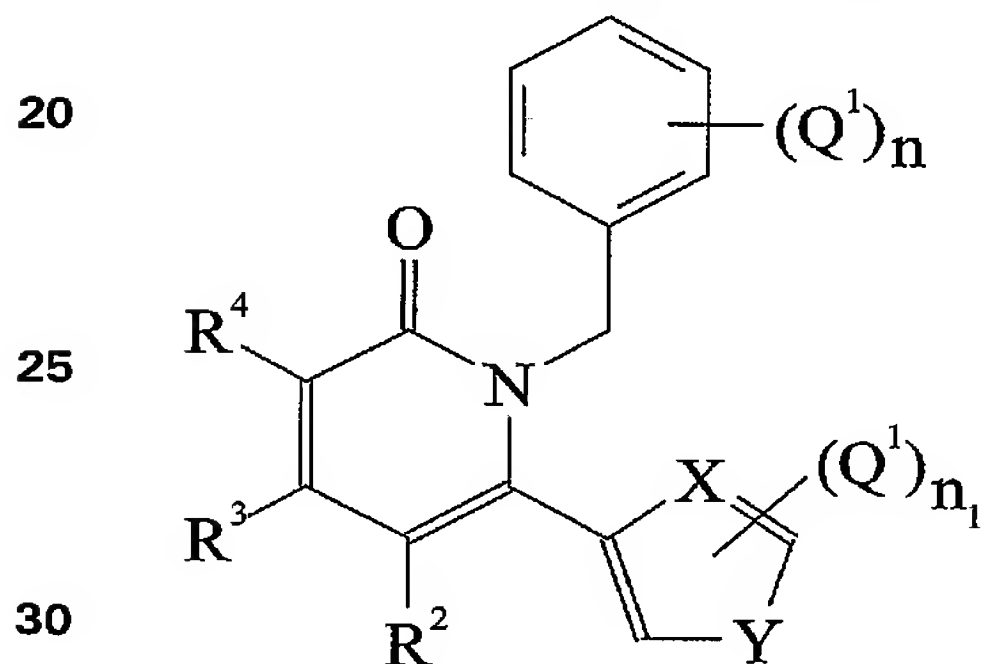
-63-

In another embodiment, the compounds for use in the compositions and methods provided herein have formula XIII:



15 wherein the variables are as defined above.

In another embodiment, the compounds for use in the compositions and methods provided herein have formula XIV:

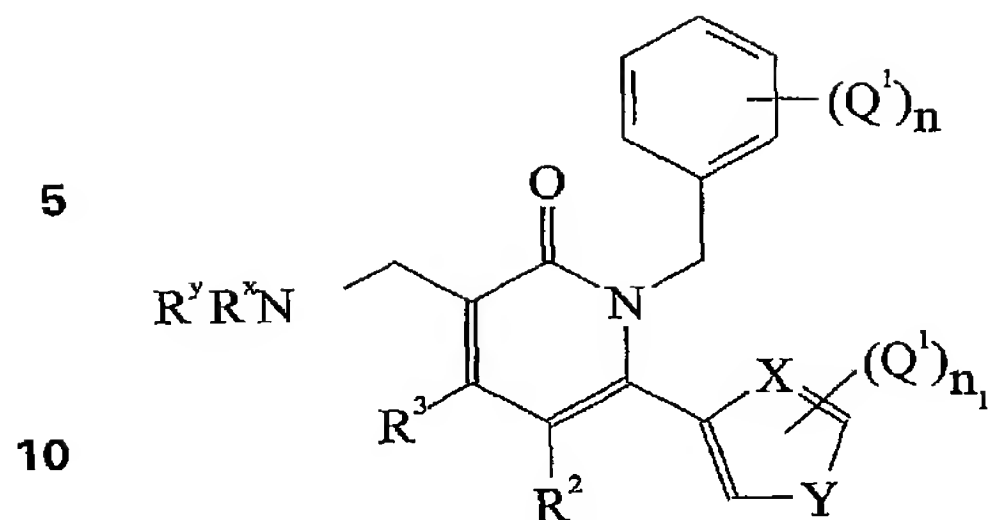


wherein the variables are defined above.

In another embodiment, the compounds for use in the compositions and methods provided herein have formula XV:

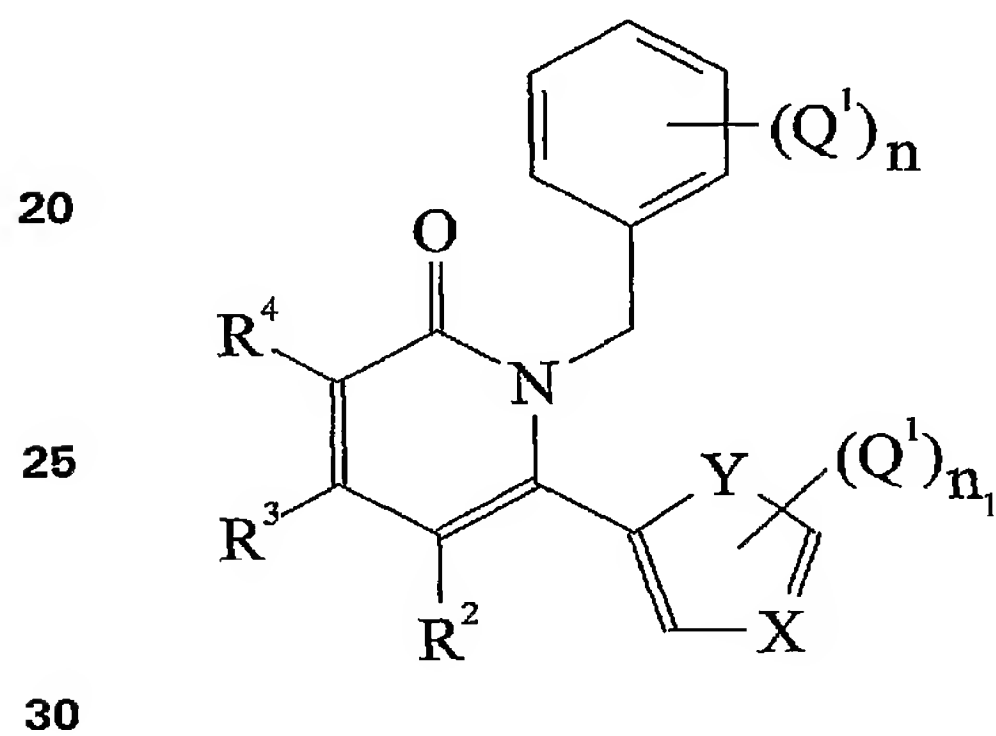
40

-64-



wherein the variables are as defined above.

15 In another embodiment, the compounds for use in the compositions and methods provided herein have formula XVI:

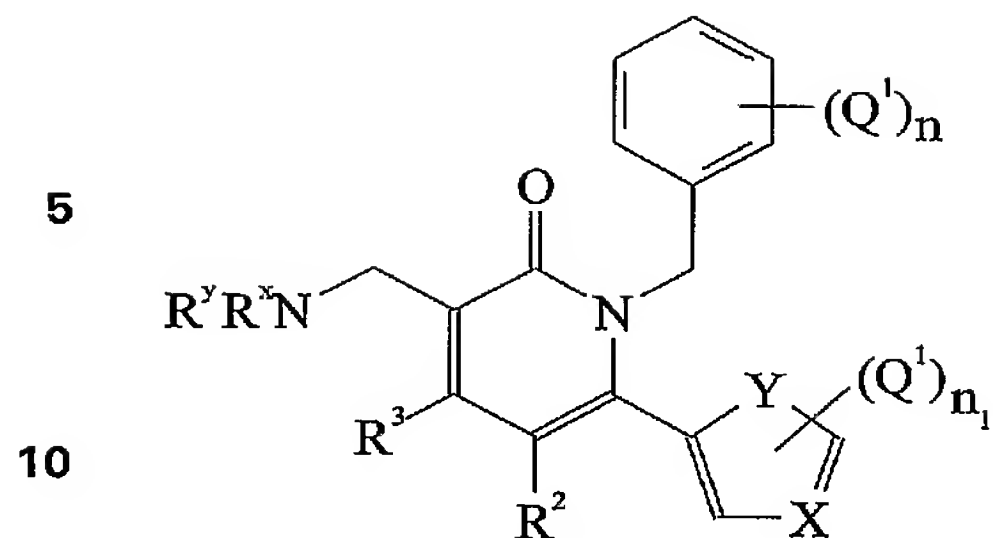


wherein the variables are as defined above.

35 In another embodiment, the compounds for use in the compositions and methods provided herein have formula XVII:

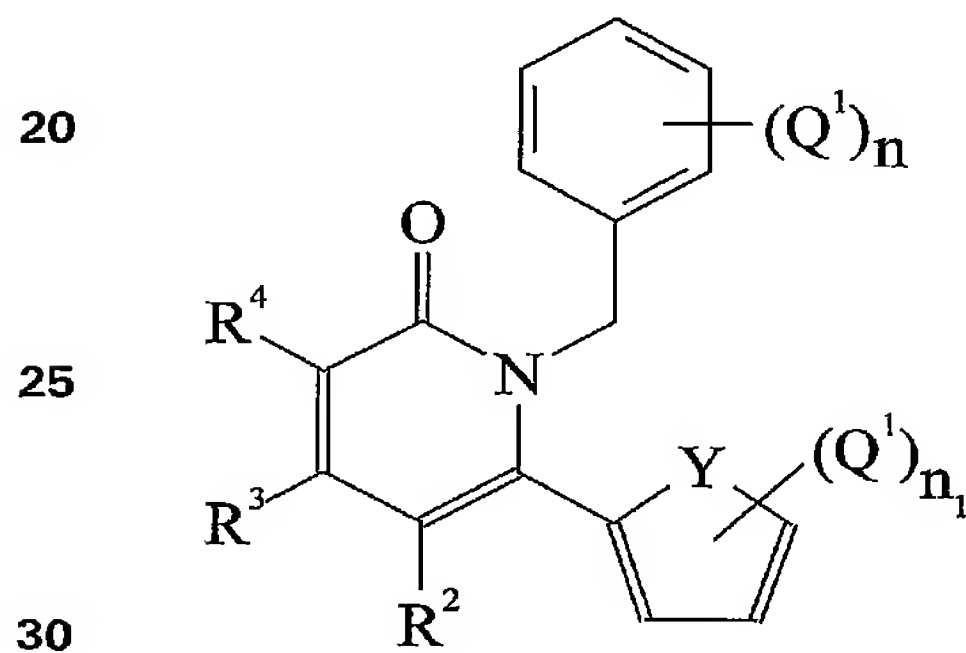
40

-65-



wherein the variables are as defined above.

15 In another embodiment, the compounds for use in the compositions and methods provided herein have formula XVII:

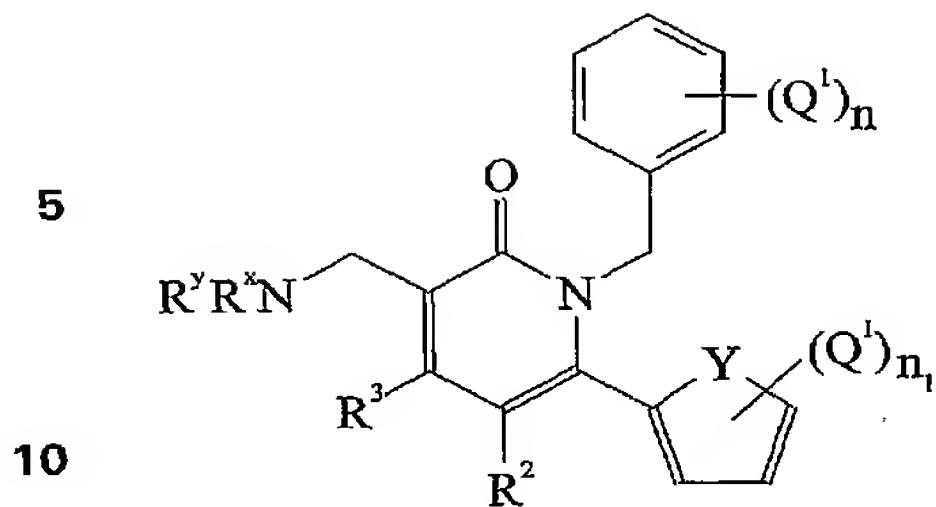


wherein the variables are as defined above.

35 In another embodiment, the compounds for use in the compositions and methods provided herein have formula XVIII:

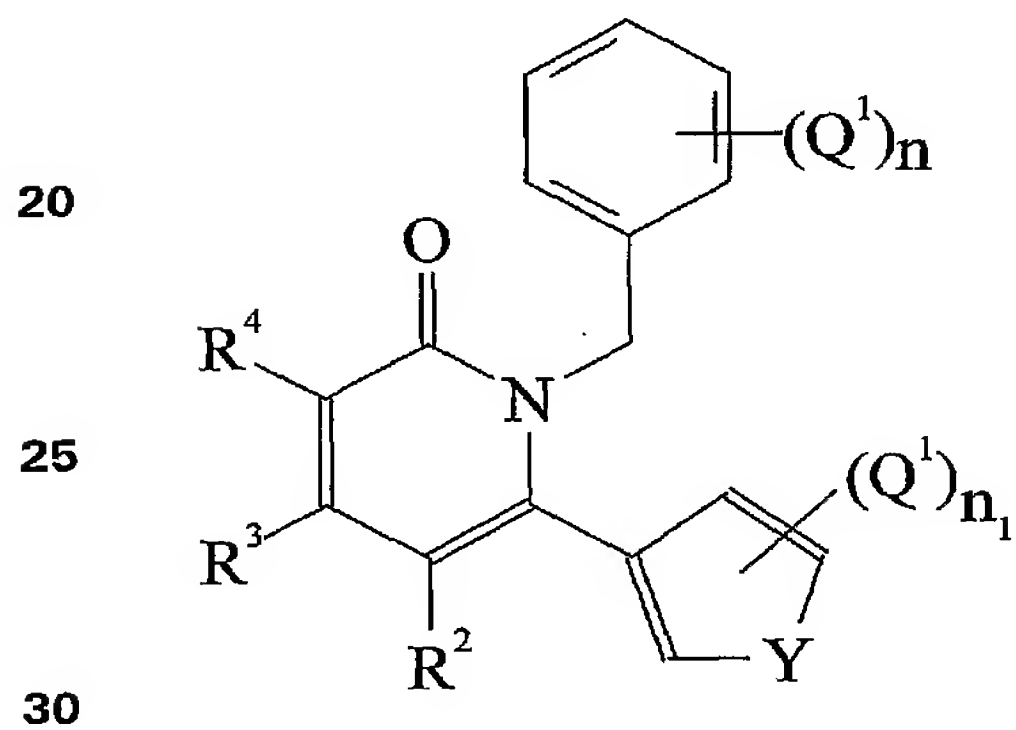
40

-66-



wherein the variables are as defined above.

15 In another embodiment, the compounds for use in the compositions and methods provided herein have formula XIX:

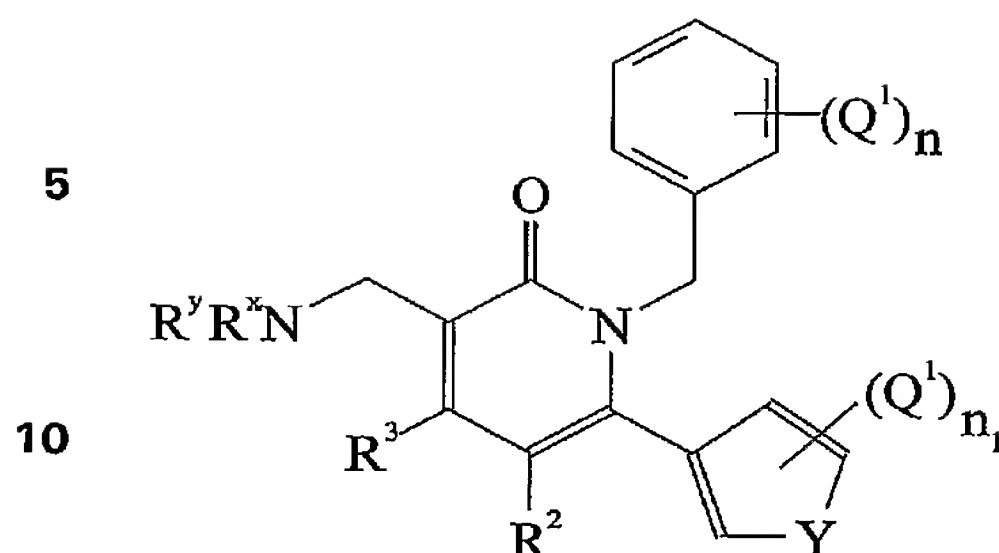


wherein the variables are as defined above.

35 In another embodiment, the compounds for use in the compositions and methods provided herein have formula XX:

40

-67-



15 wherein the variables are as defined above.

In another embodiment, the compounds for use in the compositions and methods provided herein are selected from Figure 1.

In another embodiment, the compounds for use in the compositions and methods provided herein are selected from:

- 20 1-Cyclohexylideneamino-2-oxo-6-phenyl-4-trifluoromethyl-1,2-dihydropyridine-3-carbonitrile;
- 1-Isopropylideneamino-2-oxo-6-phenyl-4-trifluoromethyl-1,2-dihydropyridine-3-carbonitrile;
- 2-Oxo-6-phenyl-1-(3,3,5,5-tetramethyl-cyclohexylideneamino)-4-
- 25 trifluoromethyl-1,2-dihydropyridine-3-carbonitrile;
- 1-(4,4-Dimethyl-cyclohex-2-enylideneamino)-2-oxo-6-phenyl-4-trifluoromethyl-1,2-dihydropyridine-3-carbonitrile (isomer 1);
- 1-(4,4-Dimethyl-cyclohex-2-enylideneamino)-2-oxo-6-phenyl-4-trifluoromethyl-1,2-dihydropyridine-3-carbonitrile (isomer 2);
- 30 1-(3-Methyl-cyclohex-2-enylideneamino)-2-oxo-6-phenyl-4-trifluoromethyl-1,2-dihydropyridine-3-carbonitrile;
- 2-Oxo-6-phenyl-1-(1-phenyl-ethylideneamino)-4-trifluoromethyl-1,2-dihydropyridine-3-carbonitrile;

-68-

- 1-(Benzylidene-amino)-2-oxo-6-phenyl-4-trifluoromethyl-1,2-dihydropyridine-3-carbonitrile;
- 1-(1-Ethyl-propylideneamino)-2-oxo-6-phenyl-4-trifluoromethyl-1,2-dihydropyridine-3-carbonitrile;
- 5 1-(4-Methyl-cyclohexylideneamino)-2-oxo-6-phenyl-4-trifluoromethyl-1,2-dihydropyridine-3-carbonitrile;
- 1-(4-Ethyl-cyclohexylideneamino)-2-oxo-6-phenyl-4-trifluoromethyl-1,2-dihydropyridine-3-carbonitrile;
- 1-(4-tert-Butyl-cyclohexylideneamino)-2-oxo-6-phenyl-4-trifluoromethyl-
- 10 1,2-dihydropyridine-3-carbonitrile;
- 1-(2-Methyl-cyclohexylideneamino)-2-oxo-6-phenyl-4-trifluoromethyl-1,2-dihydropyridine-3-carbonitrile;
- 1-Cycloheptylideneamino-2-oxo-6-phenyl-4-trifluoromethyl-1,2-dihydropyridine-3-carbonitrile;
- 15 1-Cyclopentylideneamino-2-oxo-6-phenyl-4-trifluoromethyl-1,2-dihydropyridine-3-carbonitrile;
- 1-(2-Methyl-cyclopentylideneamino)-2-oxo-6-phenyl-4-trifluoromethyl-1,2-dihydropyridine-3-carbonitrile;
- 1-(3-Methyl-cyclopentylideneamino)-2-oxo-6-phenyl-4-trifluoromethyl-1,2-
- 20 dihydropyridine-3-carbonitrile;
- 1-(Bicyclo[2.2.1]hept-2-ylideneamino)-2-oxo-6-phenyl-4-trifluoromethyl-1,2-dihydropyridine-3-carbonitrile;
- 1-(Adamantan-2-ylideneamino)-2-oxo-6-phenyl-4-trifluoromethyl-1,2-dihydropyridine-3-carbonitrile;
- 25 1-(1-Methyl-piperidin-4-ylideneamino)-2-oxo-6-phenyl-4-trifluoromethyl-1,2-dihydropyridine-3-carbonitrile;
- 4-(3-Cyano-2-oxo-6-phenyl-4-trifluoromethyl-2H-pyridin-1-ylimino)-cyclohexanecarboxylic acid ethyl ester;

- 2-Oxo-6-phenyl-1-(tetrahydro-pyran-4-ylideneamino)-4-trifluoromethyl-1,2-dihydropyridine-3-carbonitrile;
1-Amino-2-oxo-6-phenyl-4-trifluoromethyl-1,2-dihydropyridine-3-carbonitrile;
- 5 1-Amino-2-oxo-4,6-diphenyl-1,2-dihydropyridine-3-carbonitrile;
1-sec-Butylideneamino-2-oxo-6-phenyl-4-trifluoromethyl-1,2-dihydropyridine-3-carbonitrile;
1-(1,2-Dimethyl-propylideneamino)-2-oxo-6-phenyl-4-trifluoromethyl-1,2-dihydropyridine-3-carbonitrile;
- 10 1-(1-Methyl-butylideneamino)-2-oxo-6-phenyl-4-trifluoromethyl-1,2-dihydropyridine-3-carbonitrile;
1-Butylideneamino-2-oxo-6-phenyl-4-trifluoromethyl-1,2-dihydropyridine-3-carbonitrile;
1-Isobutylideneamino-2-oxo-6-phenyl-4-trifluoromethyl-1,2-
- 15 dihydropyridine-3-carbonitrile;
1-(2-Methyl-butylideneamino)-2-oxo-6-phenyl-4-trifluoromethyl-1,2-dihydropyridine-3-carbonitrile;
1-(2-Ethyl-butylideneamino)-2-oxo-6-phenyl-4-trifluoromethyl-1,2-dihydropyridine-3-carbonitrile;
- 20 1-(3-Methyl-butylideneamino)-2-oxo-6-phenyl-4-trifluoromethyl-1,2-dihydropyridine-3-carbonitrile;
1-(2,2-Dimethyl-propylideneamino)-2-oxo-6-phenyl-4-trifluoromethyl-1,2-dihydropyridine-3-carbonitrile;
1-(1-Acetyl-piperidin-4-ylideneamino)-2-oxo-6-phenyl-4-trifluoromethyl-
- 25 1,2-dihydropyridine-3-carbonitrile;
1-[(Naphthalen-2-ylmethylene)-amino]-2-oxo-6-phenyl-4-trifluoromethyl-1,2-dihydropyridine-3-carbonitrile;
1-[(2-Hydroxy-benzylidene)-amino]-2-oxo-6-phenyl-4-trifluoromethyl-1,2-dihydropyridine-3-carbonitrile;

-70-

- 1-[(2-Hydroxy-5-chloro-benzylidene)-amino]-2-oxo-6-phenyl-4-trifluoromethyl-1,2-dihydropyridine-3-carbonitrile;
- 1-[(4-Bromo-benzylidene)-amino]-2-oxo-6-phenyl-4-trifluoromethyl-1,2-dihydropyridine-3-carbonitrile;
- 5 1-[(2-Hydroxy-4-bromo-benzylidene)-amino]-2-oxo-6-phenyl-4-trifluoromethyl-1,2-dihydropyridine-3-carbonitrile;
- 1-[(2-Methyl-benzylidene)-amino]-2-oxo-6-phenyl-4-trifluoromethyl-1,2-dihydropyridine-3-carbonitrile;
- 1-[(4-Methoxy-benzylidene)-amino]-2-oxo-6-phenyl-4-trifluoromethyl-1,2-
- 10 dihydropyridine-3-carbonitrile;
- 1-Cyclohexylideneamino-2-oxo-6-phenyl-4-trifluoromethyl-1,2-dihydropyridine-3-carbonitrile;
- 1-Cyclohexylideneamino-2-oxo-4,6-diphenyl-1,2-dihydropyridine-3-carbonitrile;
- 15 1-(2-Methyl-cyclohexylideneamino)-2-oxo-4,6-diphenyl-1,2-dihydropyridine-3-carbonitrile;
- 1-(1,2-Dimethyl-propylideneamino)-2-oxo-4,6-diphenyl-1,2-dihydropyridine-3-carbonitrile;
- 1-Cyclohexylideneamino-2-oxo-6-*o*-tolyl-4-trifluoromethyl-1,2-
- 20 dihydropyridine-3-carbonitrile;
- 1-(2-Methyl-cyclohexylideneamino)-2-oxo-6-*o*-tolyl-4-trifluoromethyl-1,2-dihydropyridine-3-carbonitrile;
- 1-(1,2-Dimethyl-propylideneamino)-2-oxo-6-*o*-tolyl-4-trifluoromethyl-1,2-dihydropyridine-3-carbonitrile;
- 25 1-Cyclohexylideneamino-2-oxo-6-*m*-tolyl-4-trifluoromethyl-1,2-dihydropyridine-3-carbonitrile;
- 1-Cyclohexylideneamino-6-(2-methoxy-phenyl)-2-oxo-4-trifluoromethyl-1,2-dihydropyridine-3-carbonitrile;

-71-

- 1-(2-Methyl-cyclohexylideneamino)-6-(2-methoxy-phenyl)-2-oxo-4-trifluoromethyl-1,2-dihydropyridine-3-carbonitrile;
- 1-(1,2-Dimethyl-propylideneamino)-6-(2-methoxy-phenyl)-2-oxo-4-trifluoromethyl-1,2-dihydropyridine-3-carbonitrile;
- 5 1-(2-Methyl-cyclohexylideneamino)-2-oxo-6-m-tolyl-4-trifluoromethyl-1,2-dihydropyridine-3-carbonitrile;
- 1-(1,2-Dimethyl-propylideneamino)-2-oxo-6-m-tolyl-4-trifluoromethyl-1,2-dihydropyridine-3-carbonitrile;
- 1-Cyclohexylideneamino-2-oxo-6-*p*-tolyl-4-trifluoromethyl-1,2-
- 10 dihydropyridine-3-carbonitrile;
- 1-(2-Methyl-cyclohexylideneamino)-2-oxo-6-*p*-tolyl-4-trifluoromethyl-1,2-dihydropyridine-3-carbonitrile;
- 1-(1,2-Dimethyl-propylideneamino)-2-oxo-6-*p*-tolyl-4-trifluoromethyl-1,2-dihydropyridine-3-carbonitrile;
- 15 1-Cyclohexylideneamino-6-(3-methoxy-phenyl)-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile;
- 1-(2-Methyl-cyclohexylideneamino)-6-(3-methoxy-phenyl)-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile;
- 1-(1,2-Dimethyl-propylideneamino)-6-(3-methoxy-phenyl)-2-oxo-4-
- 20 trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile;
- 1-(2-Ethyl-cyclohexylideneamino)-2-oxo-6-phenyl-4-trifluoromethyl-1,2-dihydropyridine-3-carbonitrile;
- 2-Oxo-6-phenyl-1-(2-phenyl-cyclohexylideneamino)-4-trifluoromethyl-1,2-dihydropyridine-3-carbonitrile;
- 25 1-(2-Benzyl-cyclohexylideneamino)-2-oxo-6-phenyl-4-trifluoromethyl-1,2-dihydropyridine-3-carbonitrile;
- 1-(2,2-Dimethyl-cyclohexylideneamino)-2-oxo-6-phenyl-4-trifluoromethyl-1,2-dihydropyridine-3-carbonitrile;

-72-

- 1-(2-Chloro-cyclohexylideneamino)-2-oxo-6-phenyl-4-trifluoromethyl-1,2-dihydropyridine-3-carbonitrile;
- 1-(2-Methoxy-cyclohexylideneamino)-2-oxo-6-phenyl-4-trifluoromethyl-1,2-dihydropyridine-3-carbonitrile;
- 5 1-(2-Ethoxy-cyclohexylideneamino)-2-oxo-6-phenyl-4-trifluoromethyl-1,2-dihydropyridine-3-carbonitrile;
- 1-(2-Methylthio-cyclohexylideneamino)-2-oxo-6-phenyl-4-trifluoromethyl-1,2-dihydropyridine-3-carbonitrile;
- 2-(3-Cyano-2-oxo-6-phenyl-4-trifluoromethyl-2H-pyridin-1-ylimino)-
- 10 cyclohexanecarboxylic acid methyl ester;
- (3R)-1-(3-Methyl-cyclohexylideneamino)-2-oxo-6-phenyl-4-trifluoromethyl-1,2-dihydropyridine-3-carbonitrile;
- 2-Oxo-6-phenyl-1-phenylamino-4-trifluoromethyl-1,2-dihydropyridine-3-carbonitrile;
- 15 2-Oxo-1-phenylamino-6-*m*-tolyl-4-trifluoromethyl-1,2-dihydropyridine-3-carbonitrile;
- 1-Cyclohexylideneamino-6-(4-methoxy-phenyl)-2-oxo-4-trifluoromethyl-1,2-dihydropyridine-3-carbonitrile;
- 1-(2-Methyl-cyclohexylideneamino)-6-(4-methoxy-phenyl)-2-oxo-4-
- 20 trifluoromethyl-1,2-dihydropyridine-3-carbonitrile;
- 1-(1,2-Dimethyl-propylideneamino)-6-(4-methoxy-phenyl)-2-oxo-4-trifluoromethyl-1,2-dihydropyridine-3-carbonitrile;
- 6-(2-Chloro-phenyl)-1-cyclohexylideneamino-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile;
- 25 6-(2-Chloro-phenyl)-1-(1,2-dimethyl-propylideneamino)-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile;
- 6-(3-Chloro-phenyl)-1-cyclohexylideneamino-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile;

-73-

- 6-(3-Chloro-phenyl)-1-(2-methyl-cyclohexylideneamino)-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile;
6-(3-Chloro-phenyl)-1-(1,2-dimethyl-propylideneamino)-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile;
- 5 6-(4-Chloro-phenyl)-1-cyclohexylideneamino-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile;
6-(4-Chloro-phenyl)-1-(2-methyl-cyclohexylideneamino)-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile;
6-(4-Chloro-phenyl)-1-(1,2-dimethyl-propylideneamino)-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile;
- 10 6-(2-Chloro-phenyl)-1-(2-methyl-cyclohexylideneamino)-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile;
6-(3-Methoxy-phenyl)-1-(2-methyl-cyclohexylideneamino)-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile;
- 15 1-Cyclohexylideneamino-6-(3-hydroxy-phenyl)-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile;
1-(1,2-Dimethyl-propylideneamino)-6-(3-hydroxy-phenyl)-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile;
2-Oxo-6-phenyl-4-trifluoromethyl-3',4',5',6'-tetrahydro-2H,2'H-
- 20 [1,1']bipyridinyl-3-carbonitrile;
2-Oxo-6-phenyl-1-pyrrolidin-1-yl-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile;
1-(3-Cyano-2-oxo-6-phenyl-4-trifluoromethyl-2H-pyridin-1-yl)-3-phenyl-urea;
- 25 2-Oxo-6-m-tolyl-4-trifluoromethyl-3',4',5',6'-tetrahydro-2H,2'H-[1,1']bipyridinyl-3-carbonitrile;
2-Oxo-1-pyrrolidin-1-yl-6-m-tolyl-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile;

-74-

- 1-Amino-2-oxo-6-thiophen-2-yl-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile;
- 1-Cyclohexylideneamino-2-oxo-6-thiophen-2-yl-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile;
- 5 1-Cyclopentylideneamino-2-oxo-6-thiophen-2-yl-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile;
- 2-Oxo-1-(1-phenyl-ethylideneamino)-6-thiophen-2-yl-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile;
- 1-(1-Benzoyl-piperidin-4-ylideneamino)-2-oxo-6-thiophen-2-yl-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile;
- 10 1-(Benzylidene-amino)-2-oxo-6-thiophen-2-yl-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile;
- 1-(4-Methyl-cyclohexylideneamino)-2-oxo-6-thiophen-2-yl-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile;
- 15 1-(4-Ethyl-cyclohexylideneamino)-2-oxo-6-thiophen-2-yl-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile;
- 1-(4-tert-Butyl-cyclohexylideneamino)-2-oxo-6-thiophen-2-yl-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile;
- 1-(2-Methyl-cyclopentylideneamino)-2-oxo-6-thiophen-2-yl-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile;
- 20 1-(3-Methyl-cyclopentylideneamino)-2-oxo-6-thiophen-2-yl-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile;
- 1-(2-Methyl-cyclohexylideneamino)-2-oxo-6-thiophen-2-yl-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile;
- 25 1-Benzyl-2-oxo-6-phenyl-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile;
- 1-Benzyl-6-naphthalen-2-yl-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile;

-75-

- 1-(2-Methyl-benzyl)-2-oxo-6-phenyl-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile;
- 1-(3-Methyl-benzyl)-2-oxo-6-phenyl-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile;
- 5 1-(4-Methyl-benzyl)-2-oxo-6-phenyl-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile;
- 2-Oxo-1-phenethyl-6-phenyl-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile;
- 1-Benzyl-2-oxo-6-*m*-tolyl-4-trifluoromethyl-1,2-dihydro-pyridine-3-
- 10 carbonitrile;
- 1-(2-Methyl-benzyl)-2-oxo-6-*m*-tolyl-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile;
- 1-(3-Methyl-benzyl)-2-oxo-6-*m*-tolyl-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile;
- 15 1-(4-Methyl-benzyl)-2-oxo-6-*m*-tolyl-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile;
- 2-Oxo-1-phenethyl-6-*m*-tolyl-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile;
- 1-Benzyl-4-methyl-2-oxo-6-phenyl-1,2-dihydro-pyridine-3-carbonitrile;
- 20 1-(2-Methyl-benzyl)-4-methyl-2-oxo-6-phenyl-1,2-dihydro-pyridine-3-carbonitrile;
- 1-(3-Methyl-benzyl)-4-methyl-2-oxo-6-phenyl-1,2-dihydro-pyridine-3-carbonitrile;
- 1-(4-Methyl-benzyl)-4-methyl-2-oxo-6-phenyl-1,2-dihydro-pyridine-3-
- 25 carbonitrile;
- 4-Methyl-2-oxo-1-phenethyl-6-phenyl-1,2-dihydro-pyridine-3-carbonitrile;
- 2-Oxo-6-phenyl-1-(3-phenyl-propyl)-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile;

-76-

- 2-Oxo-6-phenyl-4-trifluoromethyl-1-(2-trifluoromethyl-benzyl)-1,2-dihydro-pyridine-3-carbonitrile;
- 2-Oxo-6-phenyl-4-trifluoromethyl-1-(3-trifluoromethyl-benzyl)-1,2-dihydro-pyridine-3-carbonitrile;
- 5 2-Oxo-6-phenyl-4-trifluoromethyl-1-(4-trifluoromethyl-benzyl)-1,2-dihydro-pyridine-3-carbonitrile;
- 1-(2-Methoxy-benzyl)-2-oxo-6-phenyl-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile;
- 1-(3-Methoxy-benzyl)-2-oxo-6-phenyl-4-trifluoromethyl-1,2-dihydro-
- 10 pyridine-3-carbonitrile;
- 1-(4-Methoxy-benzyl)-2-oxo-6-phenyl-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile;
- 1-Biphenyl-4-ylmethyl-2-oxo-6-phenyl-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile;
- 15 2-Oxo-6-*m*-tolyl-4-trifluoromethyl-1-(2-trifluoromethyl-benzyl)-1,2-dihydro-pyridine-3-carbonitrile;
- 2-Oxo-1-(3-phenyl-propyl)-6-*m*-tolyl-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile;
- 2-Oxo-6-*m*-tolyl-4-trifluoromethyl-1-(3-trifluoromethyl-benzyl)-1,2-
- 20 dihydro-pyridine-3-carbonitrile;
- 2-Oxo-6-*m*-tolyl-4-trifluoromethyl-1-(4-trifluoromethyl-benzyl)-1,2-dihydro-pyridine-3-carbonitrile;
- 1-(2-Methoxy-benzyl)-2-oxo-6-*m*-tolyl-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile;
- 25 1-(3-Methoxy-benzyl)-2-oxo-6-*m*-tolyl-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile;
- 1-(4-Methoxy-benzyl)-2-oxo-6-*m*-tolyl-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile;

-77-

- 1-Biphenyl-4-ylmethyl-2-oxo-6-*m*-tolyl-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile;
- 1-Benzyl-6-(3-methoxy-phenyl)-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile;
- 5 1-Benzyl-6-(2-chloro-phenyl)-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile;
- 1-Benzyl-6-(3-ethyl-phenyl)-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile;
- 1-Benzyl-6-(3-trifluoromethyl-phenyl)-2-oxo-4-trifluoromethyl-1,2-dihydro-10 pyridine-3-carbonitrile;
- 1-Benzyl-6-(3-nitro-phenyl)-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile;
- 1-Benzyl-6-(3-hydroxy-phenyl)-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile;
- 15 2-Oxo-1,6-diphenyl-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile;
- (1R)-2-Oxo-6-phenyl-1-(1-phenyl-ethyl)-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile;
- (1S)-2-Oxo-6-phenyl-1-(1-phenyl-ethyl)-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile;
- 20 2-Oxo-6-phenyl-1-(1,2,3,4-tetrahydro-naphthalen-1-yl)-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile;
- 1-Benzyl-6-(3-butoxy-phenyl)-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile;
- 1-Benzyl-6-(3-benzyloxy-phenyl)-2-oxo-4-trifluoromethyl-1,2-dihydro-25 pyridine-3-carbonitrile;
- 1-Benzyl-2-oxo-6-[3-(2-piperidin-1-yl-ethoxy)-phenyl]-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile;
- N-[3-(1-Benzyl-5-cyano-6-oxo-4-trifluoromethyl-1,6-dihydro-pyridin-2-yl)-phenyl]-acetamide;

-78-

- 1-[3-(1-Benzyl-5-cyano-6-oxo-4-trifluoromethyl-1,6-dihydro-pyridin-2-yl)-phenyl]-3-ethyl-urea;
- 1-(2,4-Dimethyl-benzyl)-2-oxo-6-phenyl-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile;
- 5 1-(2-Fluoro-benzyl)-2-oxo-6-phenyl-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile;
- 1-(4-Fluoro-benzyl)-2-oxo-6-phenyl-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile;
- 1-(2,4-Difluoro-benzyl)-2-oxo-6-phenyl-4-trifluoromethyl-1,2-dihydro-
- 10 pyridine-3-carbonitrile;
- 1-(4-Bromo-benzyl)-2-oxo-6-phenyl-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile;
- 4-(3-Cyano-2-oxo-6-phenyl-4-trifluoromethyl-2H-pyridin-1-ylmethyl)-benzoic acid methyl ester;
- 15 1-(2-Chloro-benzyl)-2-oxo-6-phenyl-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile;
- 1-(4-Chloro-benzyl)-2-oxo-6-phenyl-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile;
- 1-(4-Methylthio-benzyl)-2-oxo-6-phenyl-4-trifluoromethyl-1,2-dihydro-
- 20 pyridine-3-carbonitrile;
- 2-Oxo-1-(4-phenoxy-benzyl)-6-phenyl-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile;
- 1-(2,4-Dimethyl-benzyl)-2-oxo-6-*m*-tolyl-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile;
- 25 1-(2-Fluoro-benzyl)-2-oxo-6-*m*-tolyl-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile;
- 1-(4-Fluoro-benzyl)-2-oxo-6-*m*-tolyl-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile;

-79-

- 1-(2,4-Difluoro-benzyl)-2-oxo-6-*m*-tolyl-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile;
- 1-(4-Bromo-benzyl)-2-oxo-6-*m*-tolyl-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile;
- 5 4-(3-Cyano-2-oxo-6-*m*-tolyl-4-trifluoromethyl-2H-pyridin-1-ylmethyl)-benzoic acid methyl ester;
- 1-(2-Chloro-benzyl)-2-oxo-6-*m*-tolyl-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile;
- 1-(4-Chloro-benzyl)-2-oxo-6-*m*-tolyl-4-trifluoromethyl-1,2-dihydro-10 pyridine-3-carbonitrile;
- 1-(4-Methylthio-benzyl)-2-oxo-6-*m*-tolyl-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile;
- 2-Oxo-1-(4-phenoxy-benzyl)-6-*m*-tolyl-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile;
- 15 (1-Benzyl-3-cyano-2-oxo-6-phenyl-1,2-dihydro-pyridin-4-yl)-acetic acid methyl ester;
- 2-Oxo-6-phenyl-1-(4-trifluoromethoxy-benzyl)-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile;
- 2-Oxo-6-phenyl-1-pyridin-3-ylmethyl-4-trifluoromethyl-1,2-dihydro-20 pyridine-3-carbonitrile;
- 2-Oxo-6-phenyl-1-pyridin-4-ylmethyl-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile;
- 1-(4-Nitro-benzyl)-2-oxo-6-phenyl-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile;
- 25 2-Oxo-6-*m*-tolyl-1-(4-trifluoromethoxy-benzyl)-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile;
- 2-Oxo-1-pyridin-3-ylmethyl-6-*m*-tolyl-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile;

-80-

- 2-Oxo-1-pyridin-4-ylmethyl-6-*m*-tolyl-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile;
- 1-(4-Nitro-benzyl)-2-oxo-6-*m*-tolyl-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile;
- 5 1-(4-Morpholin-4-yl-benzyl)-2-oxo-6-phenyl-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile;
- [3-(1-Benzyl-5-cyano-6-oxo-4-trifluoromethyl-1,6-dihydro-pyridin-2-yl)-phenyl]-urea;
- 1-Benzyl-2-oxo-6-(3-phenethyloxy-phenyl)-4-trifluoromethyl-1,2-dihydro-
- 10 pyridine-3-carbonitrile;
- 1-Benzyl-2-oxo-6-[3-(2,2,2-trifluoro-ethoxy)-phenyl]-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile;
- 1-Benzyl-6-[3-(3-methyl-butoxy)-phenyl]-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile;
- 15 [3-(1-Benzyl-5-cyano-6-oxo-4-trifluoromethyl-1,6-dihydro-pyridin-2-yl)-phenoxy]-acetic acid methyl ester;
- 4-[3-(1-Benzyl-5-cyano-6-oxo-4-trifluoromethyl-1,6-dihydro-pyridin-2-yl)-phenoxy]-butyric acid methyl ester;
- 1-Benzyl-6-[3-(3-hydroxy-propoxy)-phenyl]-2-oxo-4-trifluoromethyl-1,2-
- 20 dihydro-pyridine-3-carbonitrile;
- 1-Benzyl-5-methyl-2-oxo-6-phenyl-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile;
- 1-Benzyl-2-oxo-4,6-diphenyl-1,2-dihydro-pyridine-3-carbonitrile;
- 4-(3-Cyano-2-oxo-6-phenyl-4-trifluoromethyl-2H-pyridin-1-ylmethyl)-
- 25 benzoic acid;
- Ethyl-carbamic acid 3-(1-benzyl-5-cyano-6-oxo-4-trifluoromethyl-1,6-dihydro-pyridin-2-yl)-phenyl ester;
- Butyl-carbamic acid 3-(1-benzyl-5-cyano-6-oxo-4-trifluoromethyl-1,6-dihydro-pyridin-2-yl)-phenyl ester;

- 1-Benzyl-6-[3-(2-methyl-benzyloxy)-phenyl]-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile;
- 1-Benzyl-6-[3-(3-methyl-benzyloxy)-phenyl]-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile;
- 5 1-Benzyl-6-[3-(4-methyl-benzyloxy)-phenyl]-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile;
- 4-[3-(1-Benzyl-5-cyano-6-oxo-4-trifluoromethyl-1,6-dihydro-pyridin-2-yl)-phenoxy-methyl]-benzoic acid methyl ester;
- 3-[3-(1-Benzyl-5-cyano-6-oxo-4-trifluoromethyl-1,6-dihydro-pyridin-2-yl)-phenoxy-methyl]-benzoic acid methyl ester;
- 10 [3-(1-Benzyl-5-cyano-6-oxo-4-trifluoromethyl-1,6-dihydro-pyridin-2-yl)-phenoxy]-acetic acid;
- 4-[3-(1-Benzyl-5-cyano-6-oxo-4-trifluoromethyl-1,6-dihydro-pyridin-2-yl)-phenoxy]-butyric acid;
- 15 N-[3-(1-Benzyl-5-cyano-6-oxo-4-trifluoromethyl-1,6-dihydro-pyridin-2-yl)-phenyl]-butyramide;
- Cyclohexanecarboxylic acid [3-(1-benzyl-5-cyano-6-oxo-4-trifluoromethyl-1,6-dihydro-pyridin-2-yl)-phenyl]-amide;
- N-[3-(1-Benzyl-5-cyano-6-oxo-4-trifluoromethyl-1,6-dihydro-pyridin-2-yl)-phenyl]-benzamide;
- 20 [3-(1-Benzyl-5-cyano-6-oxo-4-trifluoromethyl-1,6-dihydro-pyridin-2-yl)-phenyl]-carbamic acid methyl ester;
- [3-(1-Benzyl-5-cyano-6-oxo-4-trifluoromethyl-1,6-dihydro-pyridin-2-yl)-phenyl]-carbamic acid ethyl ester;
- 25 [3-(1-Benzyl-5-cyano-6-oxo-4-trifluoromethyl-1,6-dihydro-pyridin-2-yl)-phenyl]-carbamic acid phenyl ester;
- 6-(3-Amino-phenyl)-1-benzyl-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile;

-82-

- 1-Cyclohexylmethyl-2-oxo-6-phenyl-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile;
2-Oxo-6-phenyl-1-thiophen-2-ylmethyl-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile;
- 5 1-(5-Methyl-furan-2-ylmethyl)-2-oxo-6-phenyl-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile;
2-Oxo-6-phenyl-1-(2,3,5-trifluoro-benzyl)-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile;
1-(4-Chloro-2-methyl-benzyl)-2-oxo-6-phenyl-4-trifluoromethyl-1,2-
- 10 dihydro-pyridine-3-carbonitrile;
1-(3,4-Dichloro-benzyl)-2-oxo-6-phenyl-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile;
1-(3-Fluoro-benzyl)-2-oxo-6-phenyl-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile;
- 15 1-(4-Methyl-benzyl)-6-*m*-tolyl-1H-pyridin-2-one;
1-(4-Methyl-benzyl)-6-phenyl-1H-pyridin-2-one;
1-Benzyl-6-*m*-tolyl-1H-pyridin-2-one;
1-Benzyl-6-phenyl-1H-pyridin-2-one;
2-Oxo-6-phenyl-1-(2,3,4-trifluoro-benzyl)-4-trifluoromethyl-1,2-dihydro-
- 20 pyridine-3-carbonitrile;
1-Cyclohexylmethyl-2-oxo-6-*m*-tolyl-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile;
2-Oxo-1-thiophen-2-ylmethyl-6-*m*-tolyl-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile;
- 25 2-Oxo-6-*m*-tolyl-1-(2,3,5-trifluoro-benzyl)-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile;
1-(4-Chloro-2-methyl-benzyl)-2-oxo-6-*m*-tolyl-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile;

-83-

- 1-(3,4-Dichloro-benzyl)-2-oxo-6-*m*-tolyl-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile;
- 1-(3-Fluoro-benzyl)-2-oxo-6-*m*-tolyl-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile;
- 5 1-(3,4-Difluoro-benzyl)-2-oxo-6-phenyl-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile;
- 1-(2,5-Difluoro-benzyl)-2-oxo-6-phenyl-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile;
- 1-(2,4-Dichloro-benzyl)-2-oxo-6-phenyl-4-trifluoromethyl-1,2-dihydro-
- 10 pyridine-3-carbonitrile;
- 1-(2,3-Dimethyl-benzyl)-2-oxo-6-phenyl-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile;
- 1-(2,5-Dimethyl-benzyl)-2-oxo-6-phenyl-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile;
- 15 1-(3,4-Dimethyl-benzyl)-2-oxo-6-phenyl-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile;
- 1-(2,3-Difluoro-benzyl)-2-oxo-6-phenyl-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile;
- 1-(2-Bromo-benzyl)-2-oxo-6-phenyl-4-trifluoromethyl-1,2-dihydro-pyridine-
- 20 3-carbonitrile;
- 1-(3-Bromo-benzyl)-2-oxo-6-phenyl-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile;
- 1-(3,4-Difluoro-benzyl)-2-oxo-6-*m*-tolyl-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile;
- 25 1-(2,5-Difluoro-benzyl)-2-oxo-6-*m*-tolyl-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile;
- 1-(2,4-Dichloro-benzyl)-2-oxo-6-*m*-tolyl-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile;

-84-

- 1-(2,3-Dimethyl-benzyl)-2-oxo-6-*m*-tolyl-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile;
1-(2,5-Dimethyl-benzyl)-2-oxo-6-*m*-tolyl-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile;
- 5 1-(3,4-Dimethyl-benzyl)-2-oxo-6-*m*-tolyl-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile;
1-(2,3-Difluoro-benzyl)-2-oxo-6-*m*-tolyl-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile;
1-(2-Bromo-benzyl)-2-oxo-6-*m*-tolyl-4-trifluoromethyl-1,2-dihydro-
- 10 pyridine-3-carbonitrile;
1-(3-Bromo-benzyl)-2-oxo-6-*m*-tolyl-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile;
N-[3-(1-Benzyl-5-cyano-6-oxo-4-trifluoromethyl-1,6-dihydro-pyridin-2-yl)-phenyl]-methanesulfonamide;
- 15 6-(3-Ethyl-phenyl)-1-(4-methyl-benzyl)-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile;
1-(4-Methyl-benzyl)-2-oxo-6-*p*-tolyl-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile;
6-(2-Chloro-phenyl)-1-(4-methyl-benzyl)-2-oxo-4-trifluoromethyl-1,2-
- 20 dihydro-pyridine-3-carbonitrile;
6-(3-Chloro-phenyl)-1-(4-methyl-benzyl)-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile;
6-(4-Chloro-phenyl)-1-(4-methyl-benzyl)-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile;
- 25 3-[5-Cyano-1-benzyl-6-oxo-4-trifluoromethyl-1,6-dihydro-pyridin-2-yl]-benzoic acid;
3-[5-Cyano-1-benzyl-6-oxo-4-trifluoromethyl-1,6-dihydro-pyridin-2-yl]-benzoic acid tert-butyl ester;

- 1-Benzyl-6-(3-bromomethyl-phenyl)-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile;
2-Oxo-6-phenyl-1-(2,2,2-trifluoro-ethyl)-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile;
- 5 1-Benzyl-3-bromo-6-phenyl-1H-pyridin-2-one;
1-Biphenyl-4-ylmethyl-6-phenyl-1H-pyridin-2-one;
1-Benzyl-2-oxo-6-phenyl-1,2-dihydro-pyridine-3-carbonitrile;
3-(1-Benzyl-5-cyano-6-oxo-4-trifluoromethyl-1,6-dihydro-pyridin-2-yl)-N,N-diethyl-benzamide;
- 10 1-Benzyl-2-oxo-6-(3-phenoxyethyl-phenyl)-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile;
1-Benzyl-6-(3-diethylaminomethyl-phenyl)-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile;
1-Benzyl-2-oxo-4-pentafluoroethyl-6-phenyl-1,2-dihydro-pyridine-3-
- 15 carbonitrile;
1-(4-Methyl-benzyl)-2-oxo-4-pentafluoroethyl-6-phenyl-1,2-dihydro-pyridine-3-carbonitrile;
1-(2,4-Dimethyl-benzyl)-2-oxo-4-pentafluoroethyl-6-phenyl-1,2-dihydro-pyridine-3-carbonitrile;
- 20 1-(2,4-Dimethyl-benzyl)-6-(3,5-dimethyl-phenyl)-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile;
1-(2,4-Dimethyl-benzyl)-2-oxo-6-(5,5,8,8-tetramethyl-5,6,7,8-tetrahydronaphthalen-2-yl)-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile;
1-(2,4-Dimethyl-benzyl)-6-(3-ethyl-phenyl)-2-oxo-4-trifluoromethyl-1,2-
- 25 dihydro-pyridine-3-carbonitrile;
1-(2,4-Dimethyl-benzyl)-2-oxo-6-p-tolyl-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile;
1-(2,4-Dimethyl-benzyl)-6-(3-methoxy-phenyl)-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile;

-86-

1-(2,4-Dimethyl-benzyl)-6-(4-methoxy-phenyl)-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile;

1-(2,4-Dimethyl-benzyl)-6-(2-chloro-phenyl)-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile;

5 1-(2,4-Dimethyl-benzyl)-6-(3-chloro-phenyl)-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile;

1-(2,4-Dimethyl-benzyl)-6-(4-chloro-phenyl)-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile; and

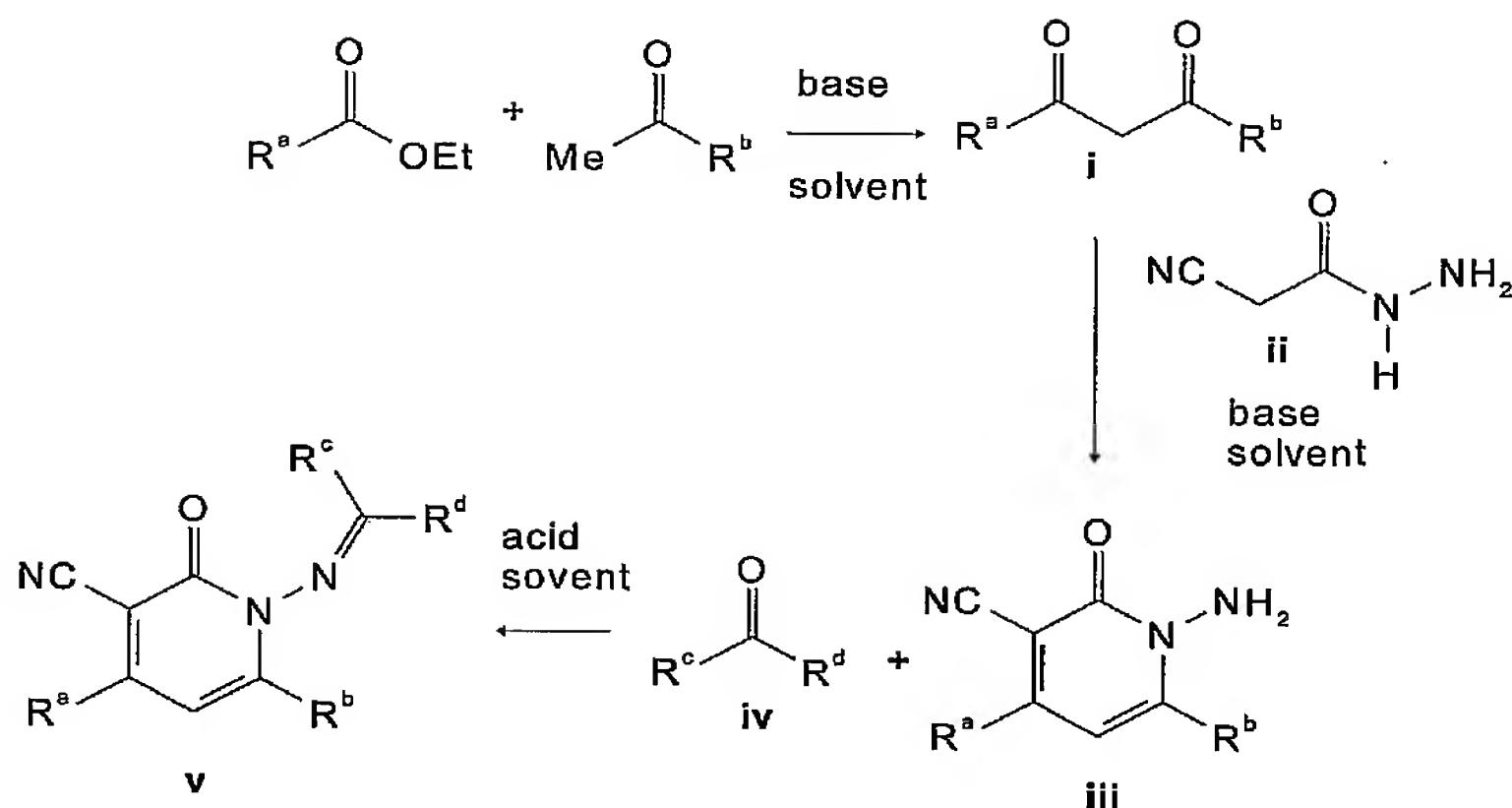
10 1-Benzyl-2-oxo-6-thiophen-2-yl-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile.

C. Preparation of the compounds

The compounds provided herein can be prepared using readily available starting materials or known intermediates. Schemes 1, 2 and 3 (*infra*) provide a summary of the synthetic routes utilized in producing the
15 compounds provided herein.

Scheme 1, below, details the synthetic strategy utilized for the construction of N-amino-2-pyridone derivatives v. Such hydrazones can be readily obtained via the condensation of N-aminopyridones iii with aldehydes ($R^c = H$) and ketones (as iv) in the presence of acids in
20 various solvents. The N-amino-2-pyridone itself is produced by a cyclocondensation reaction between 1,3-diketones i and cyanoacetohydrazide ii in the presence of various bases (see, *e.g.*, Elgemeie *et al.* (1994) *Org. Prep. Proc. Int.* 26:465-468). The requisite 1,3-dicarbonyl compounds i can be obtained from the corresponding
25 esters and methyl ketones using strong bases.

-87-

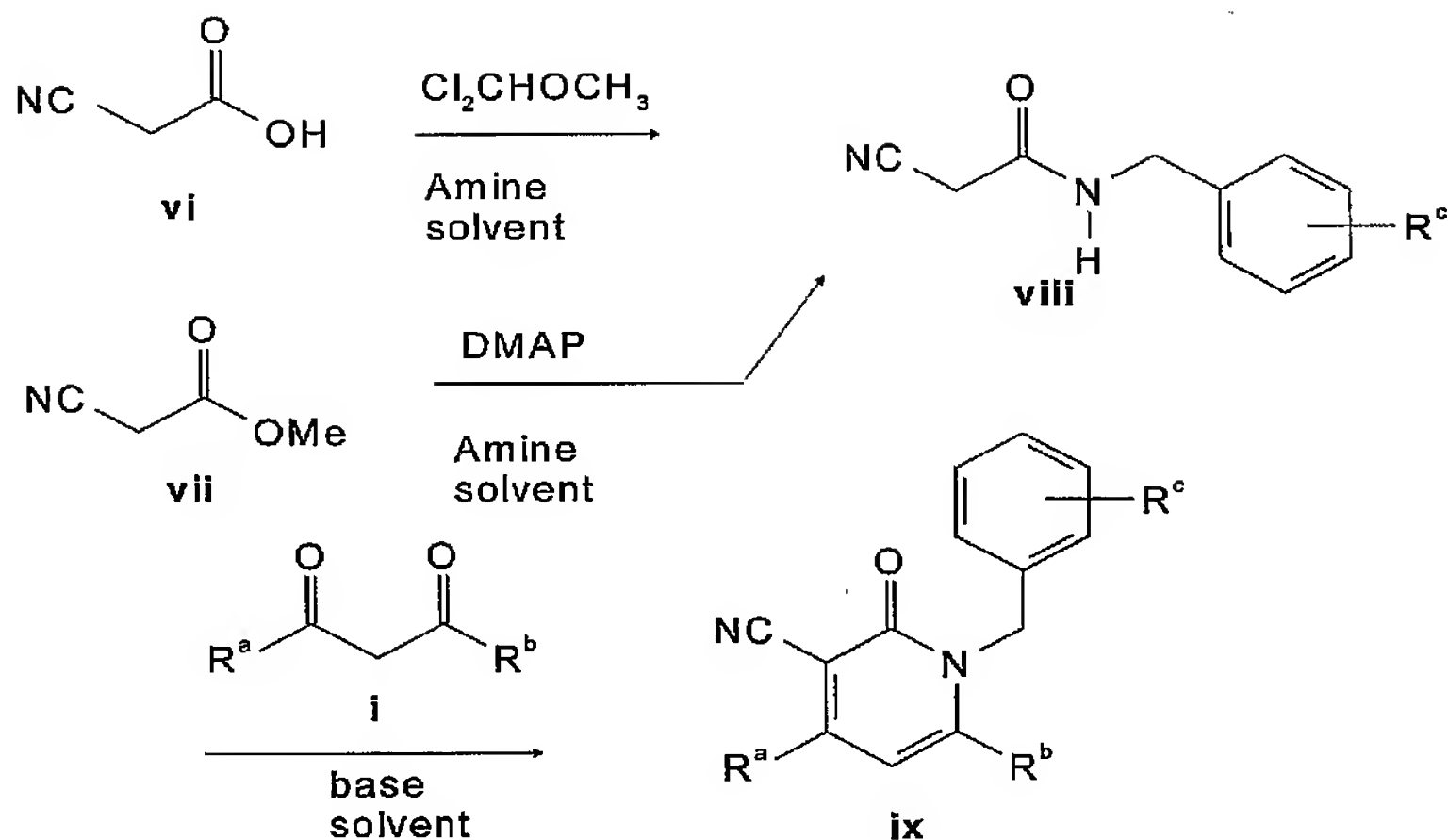


- Scheme 2, below, details the synthetic strategy utilized in constructing the N-benzyl-2-pyridone ix compounds. These compounds are formed from an analogous cyclocondensation reaction to that used to form the N-aminopyridones. Reaction of cyanoacetamides viii with 1,2-
- 5 diketones i using various bases produces N-benzyl-2-pyridones. The requisite cyanoacetamides viii are formed from either cyanoacetic acid vi or methyl cyanoacetate vii. Cyanoacetic acid is first activated to its acid chloride using the reagent α,α -dichloromethyl methyl ether. The resultant acid chloride is reacted *in situ* with various amines to affect acylation.
- 10 Direct conversion of methyl cyanoacetate vii to the corresponding cyanoacetamides viii is carried out with amines and in the presence of the acylation catalyst 4-(dimethylamino)pyridine (DMAP).

15

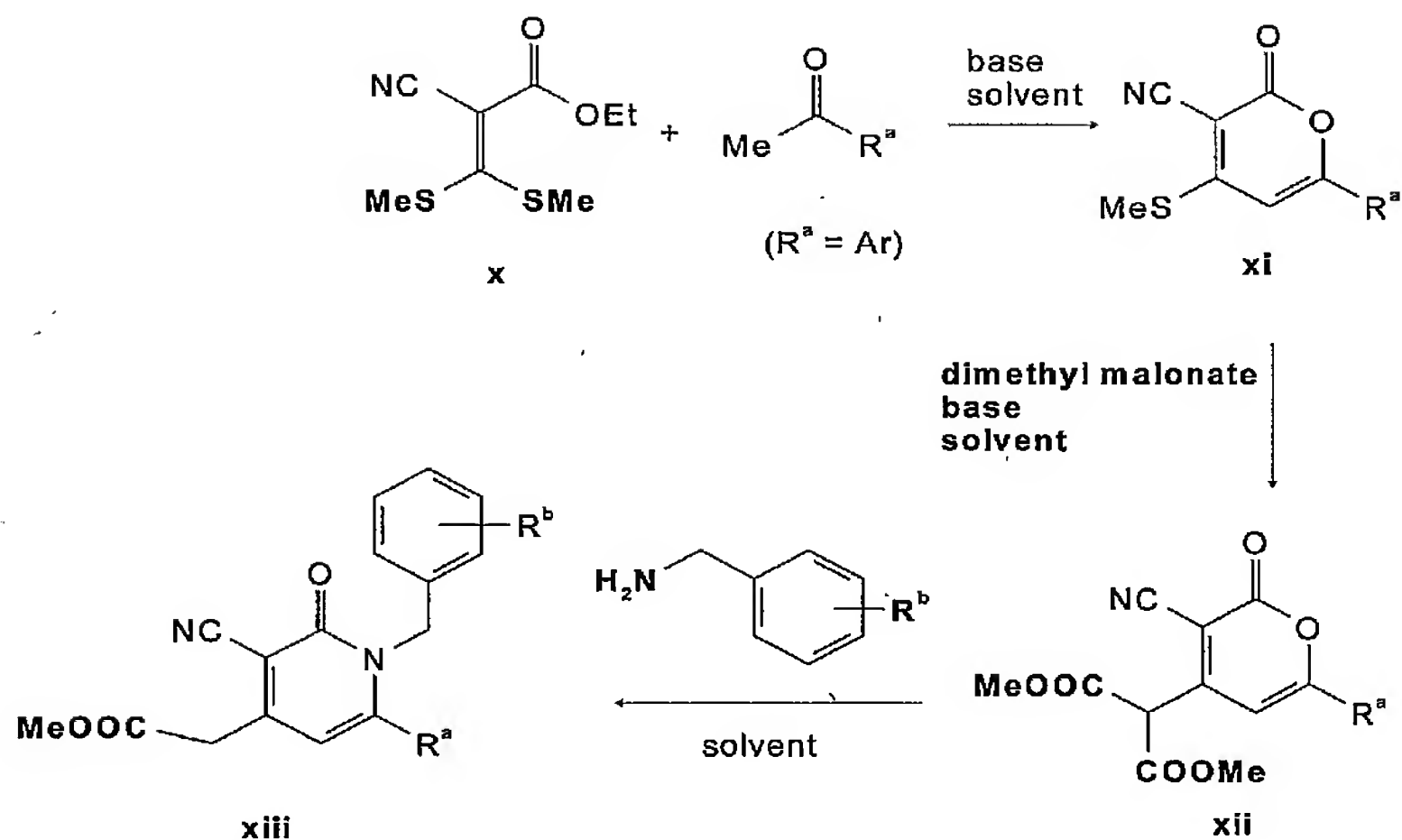
20

-88-



Scheme 3, below, details the synthetic strategy utilized to construct N-benzyl-2-pyridones containing a methoxycarbonylmethyl moiety at the C4-position of the pyridone ring. Compound **xiii** is obtained directly from the diester compound **xii** by reaction with benzylamines (for the conversion of pyrones to N-benzyl 2-pyridones, see, *e.g.*, Katrizky *et al.* (1980) *J. Chem. Soc., Perkin Trans. I*:2851-2855). Both pyridone formation and the ester cleavage (via decarboxylation) occur in this single step. The malonate substituted pyrone **xii** derives from the 4-methylsulfide variant **xi** via base-induced substitution with dimethylmalonate (see, *e.g.*, Tominaga *et al.* (1984) *Chem. Pharm. Bull.* 32:3384-3395). Compound **xi** is readily obtained via the cyclocondensation reaction between the commercially available dithiane **x** and methyl ketones.

-89-



Other methods for the preparation of the compounds provided herein are shown in the Schemes below.

Scheme 4:

5

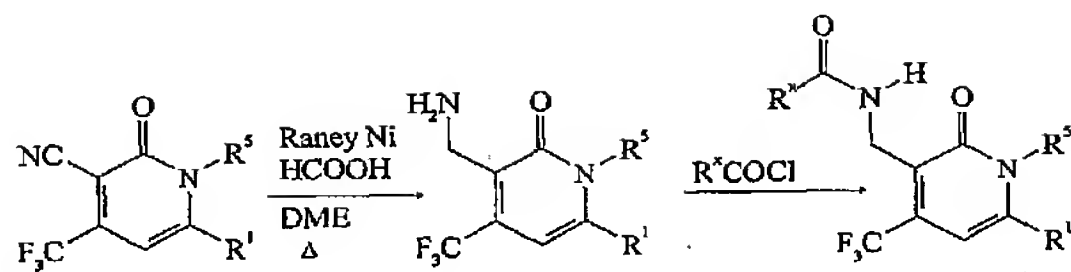
10

15

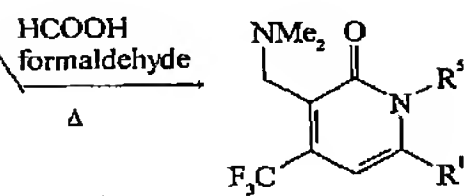
20

-90-

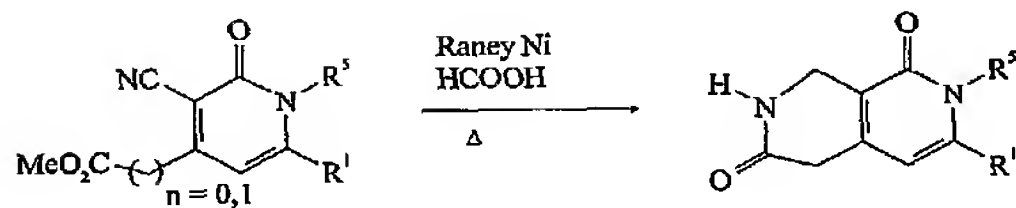
5



10



15



20

25

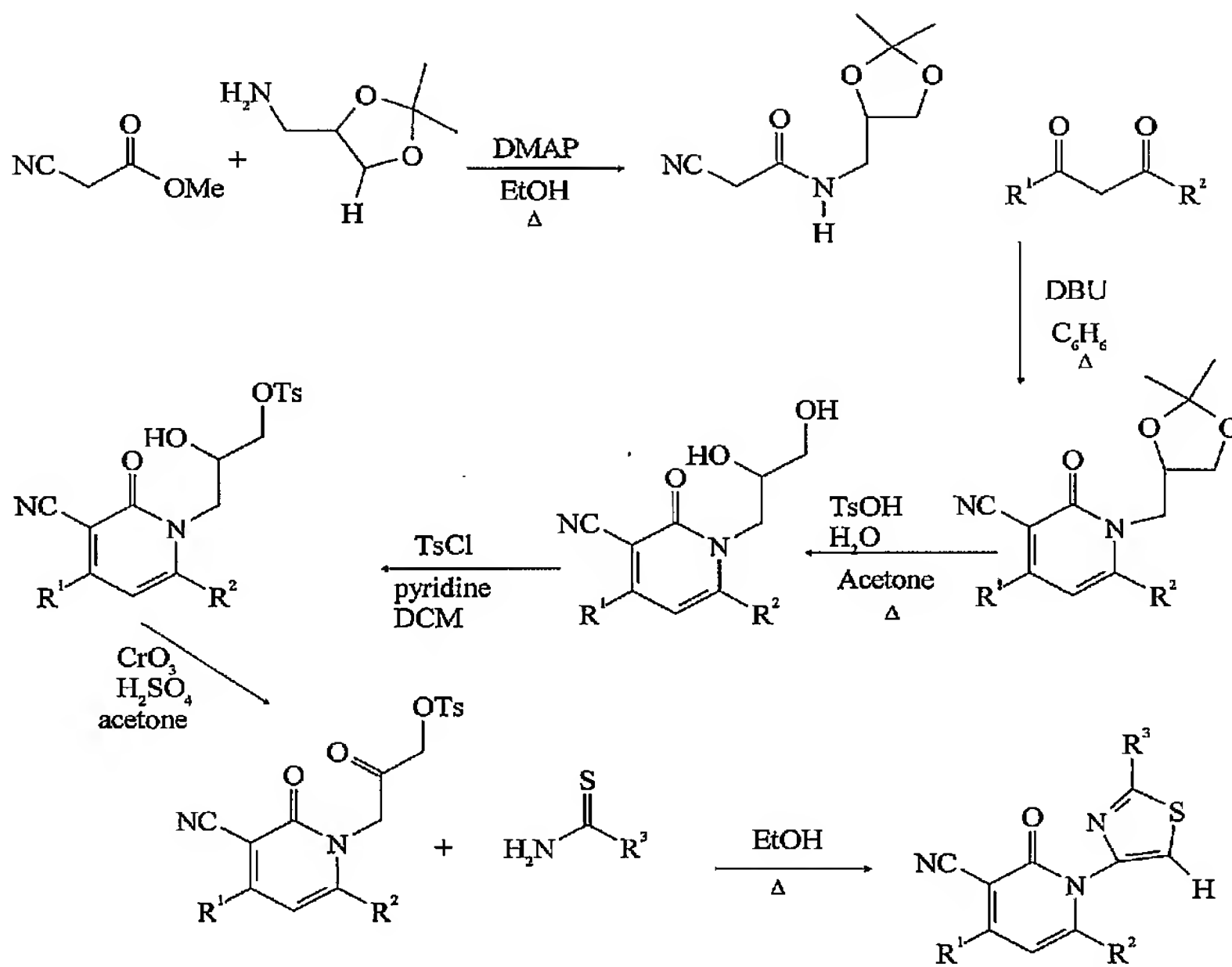
30

35

40

-91-

Scheme 5:



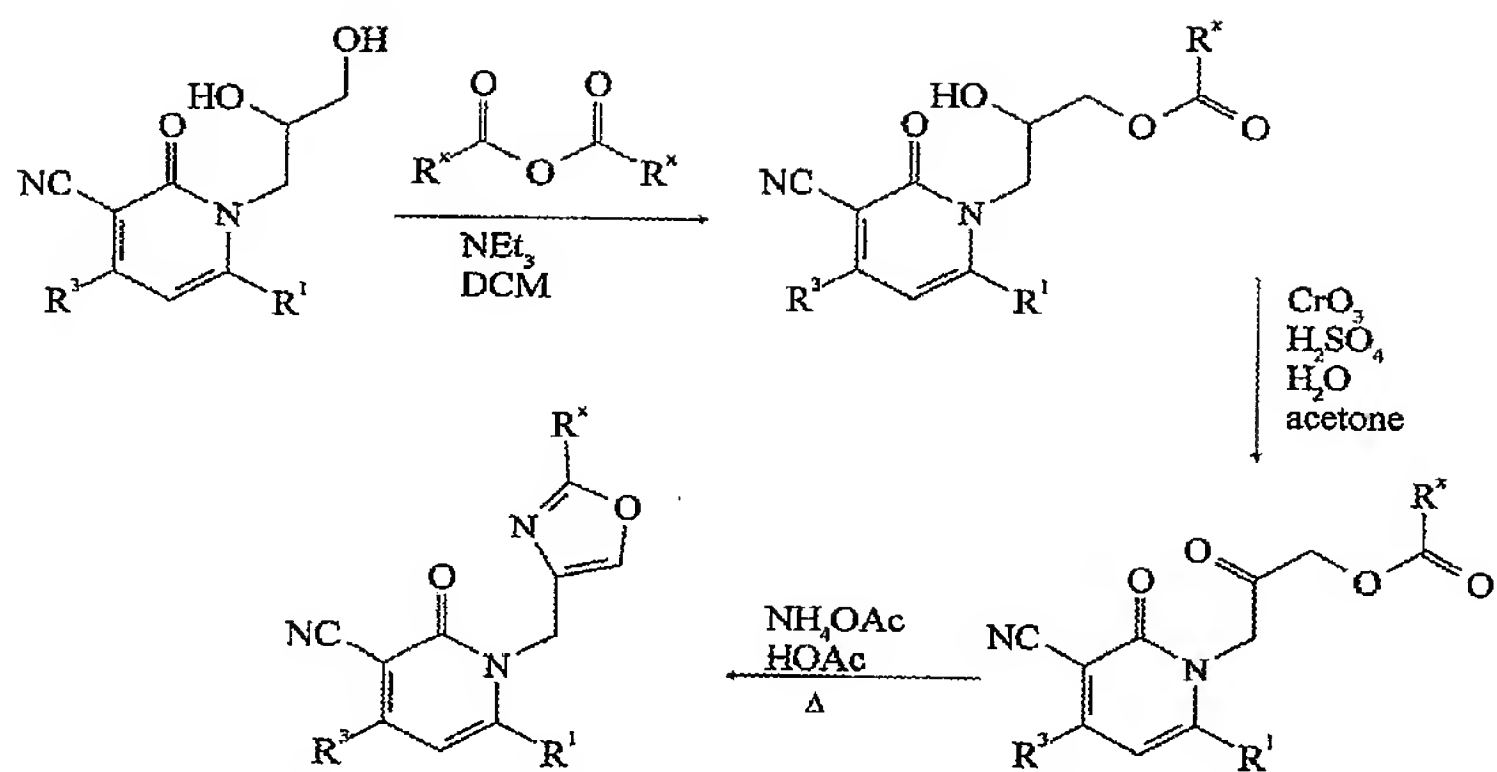
5

10

15

-92-

Scheme 6:



5

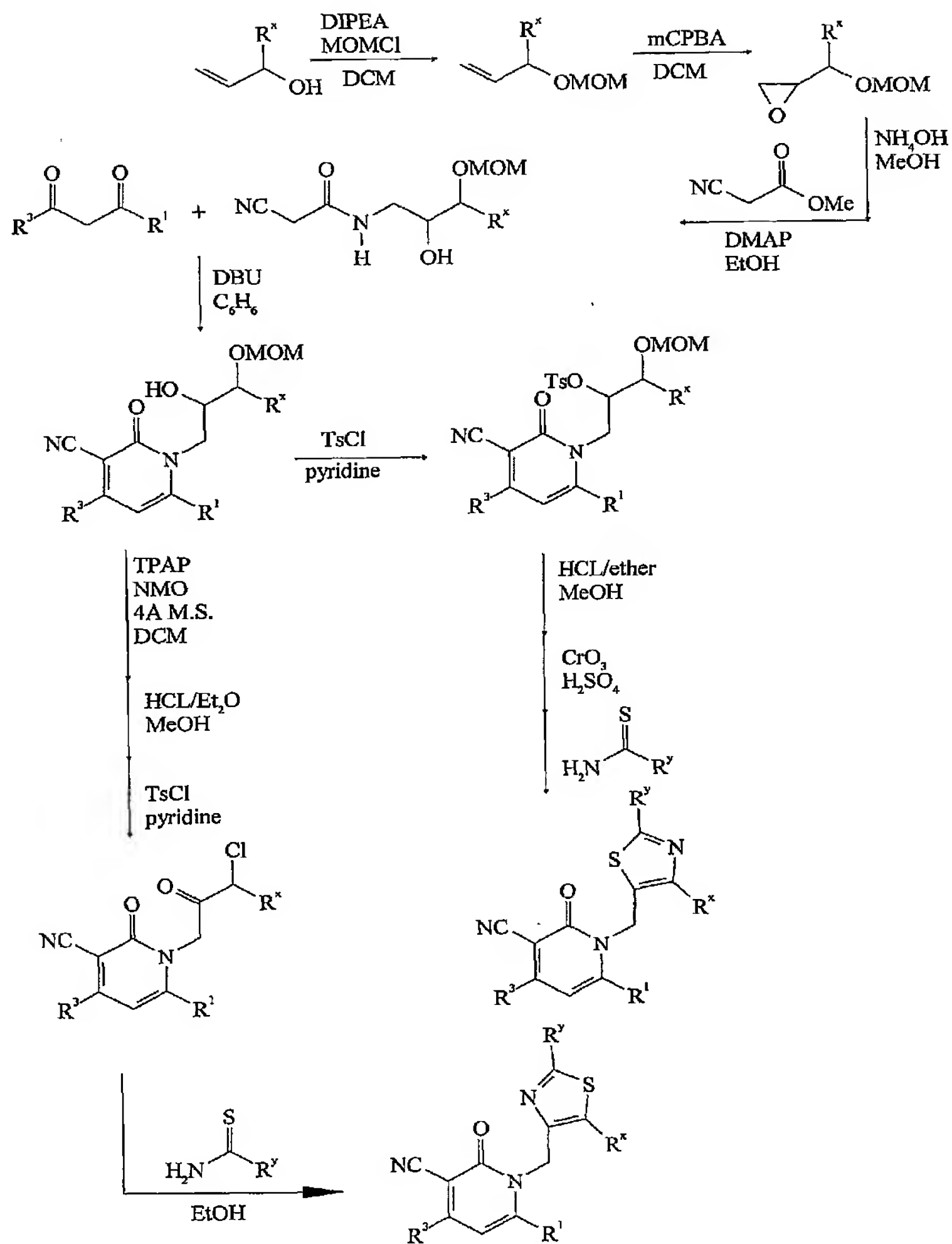
10

15

20

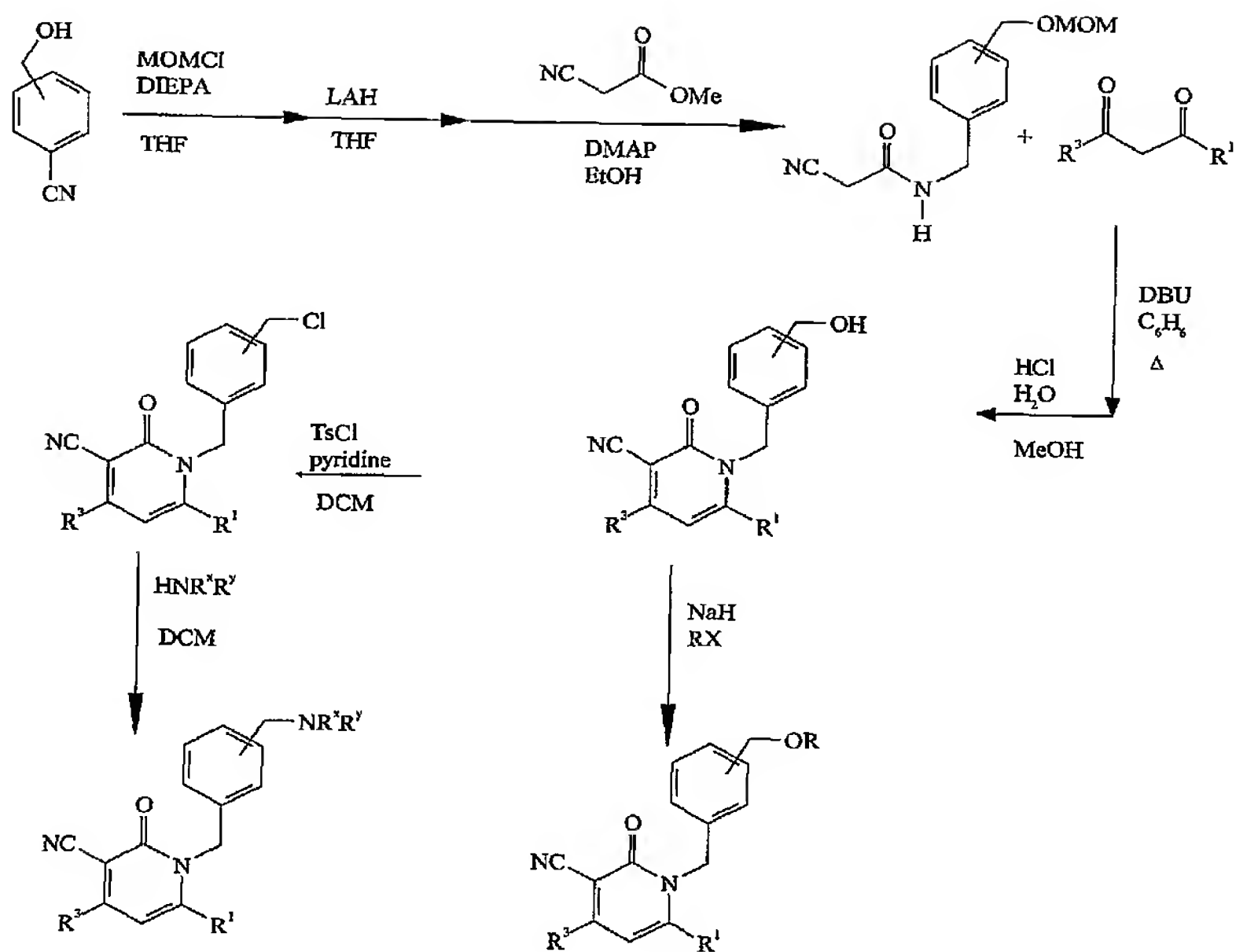
-93-

Scheme 7:



-94-

Scheme 8:



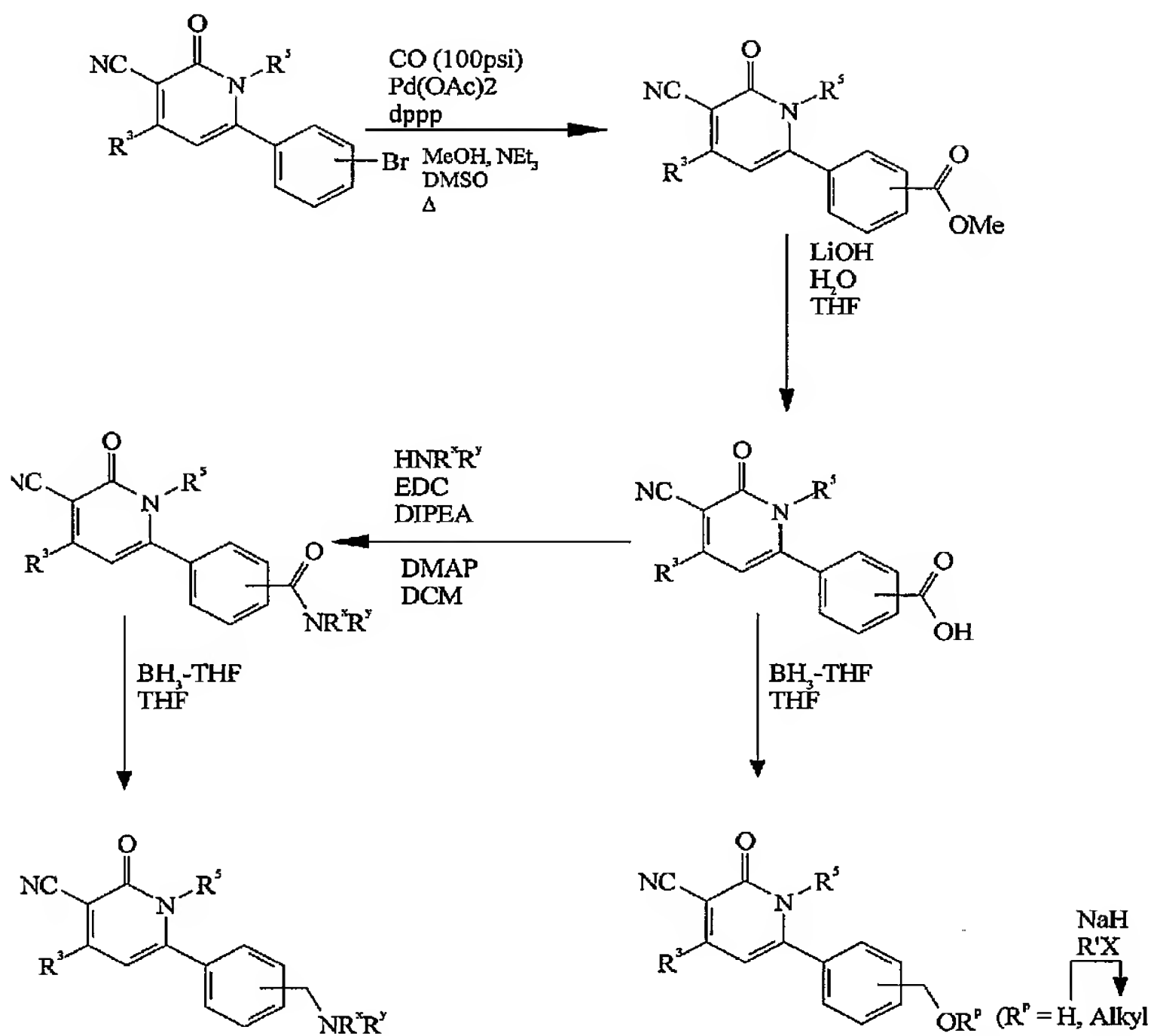
5

10

15

-95-

Scheme 9:

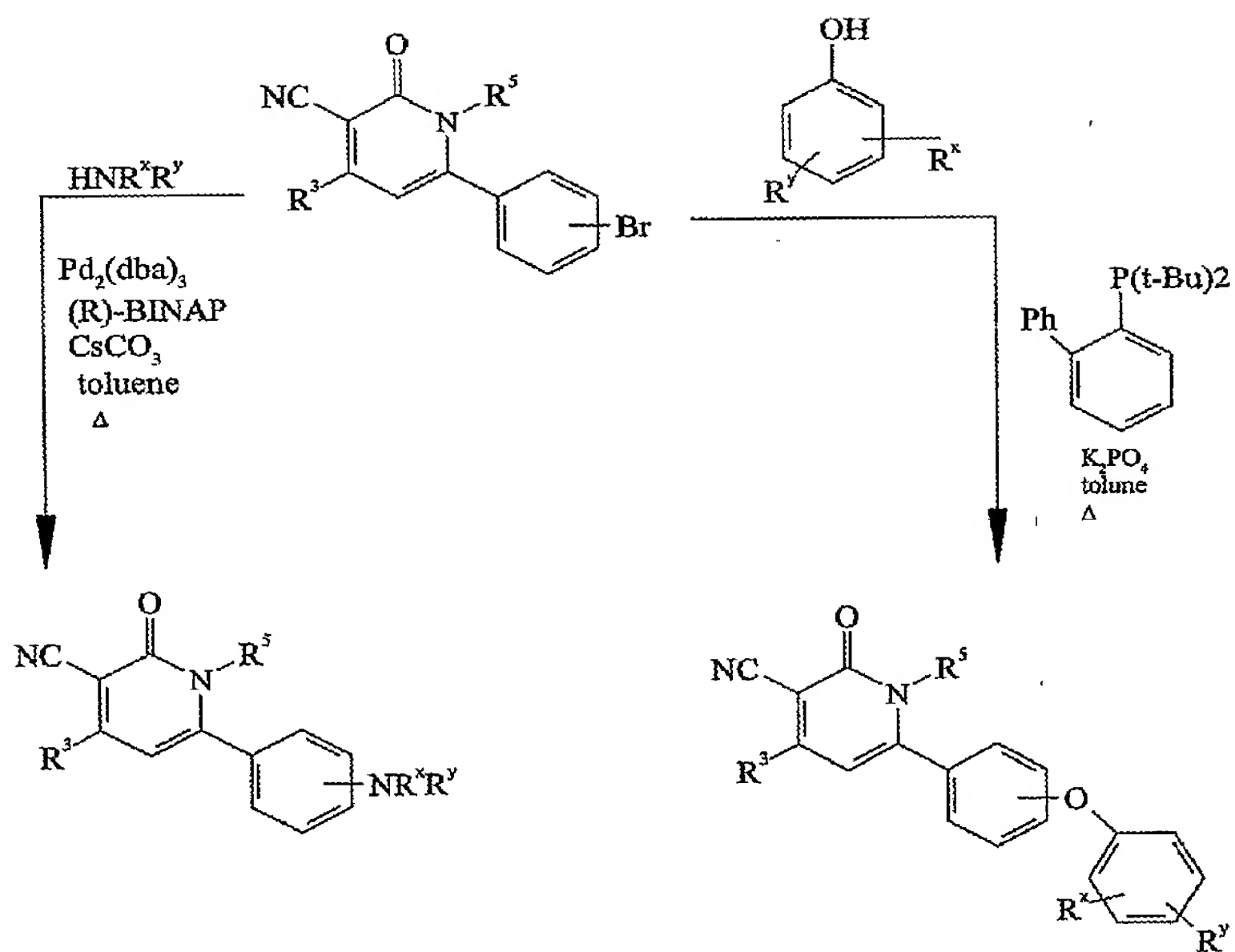


5

10

-96-

Scheme 10:



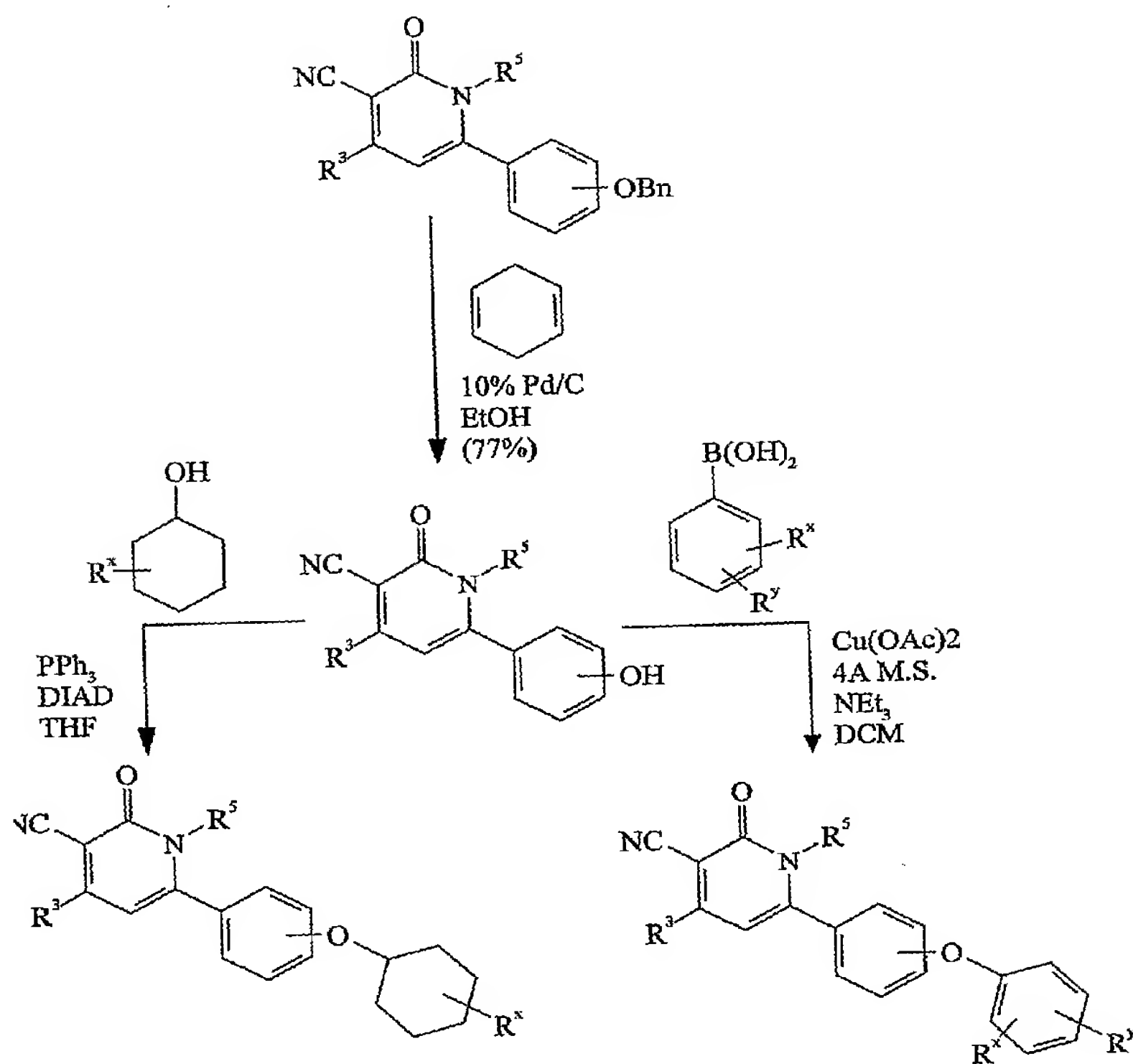
5

10

15

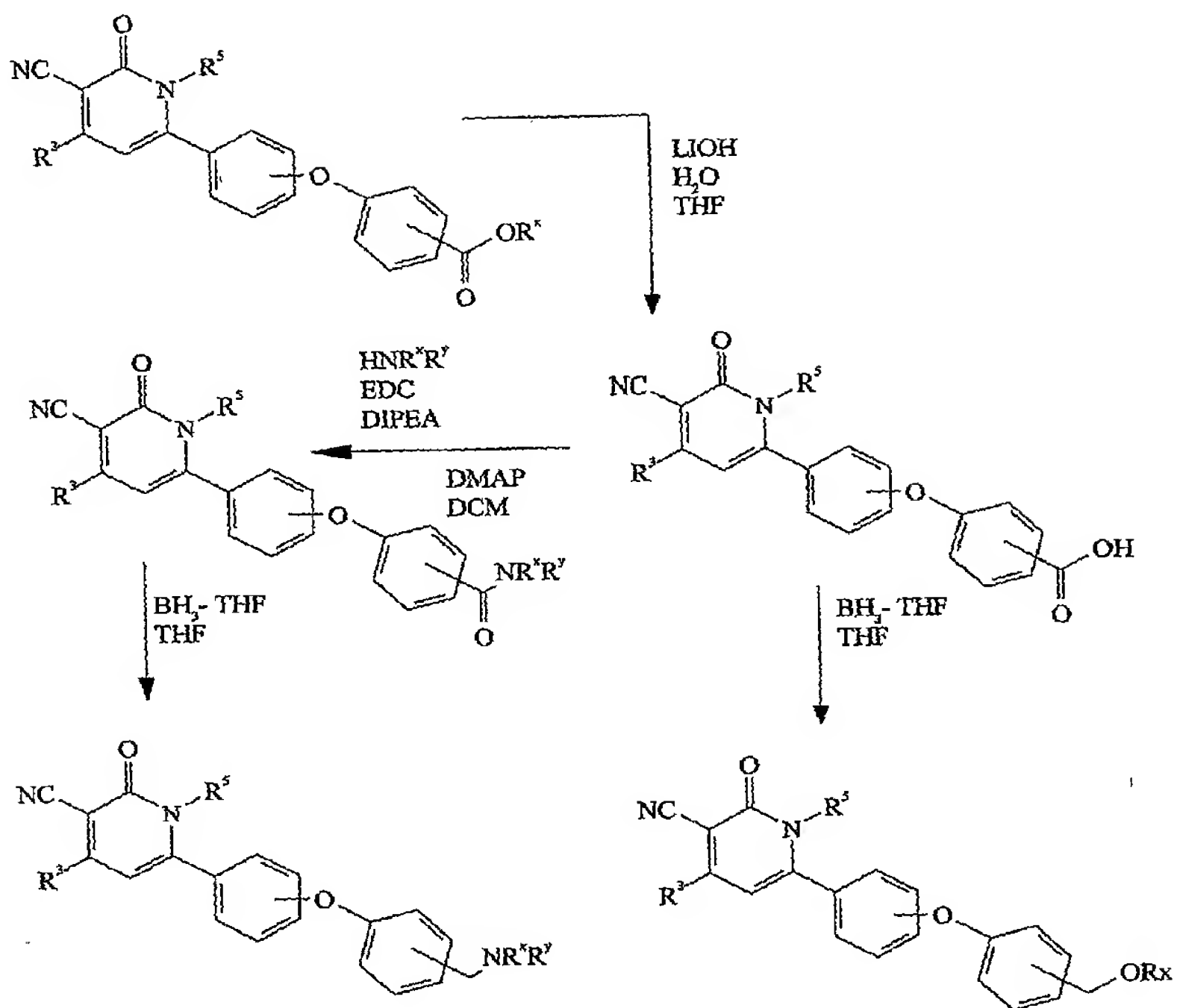
-97-

Scheme 11:



-98-

Scheme 12:

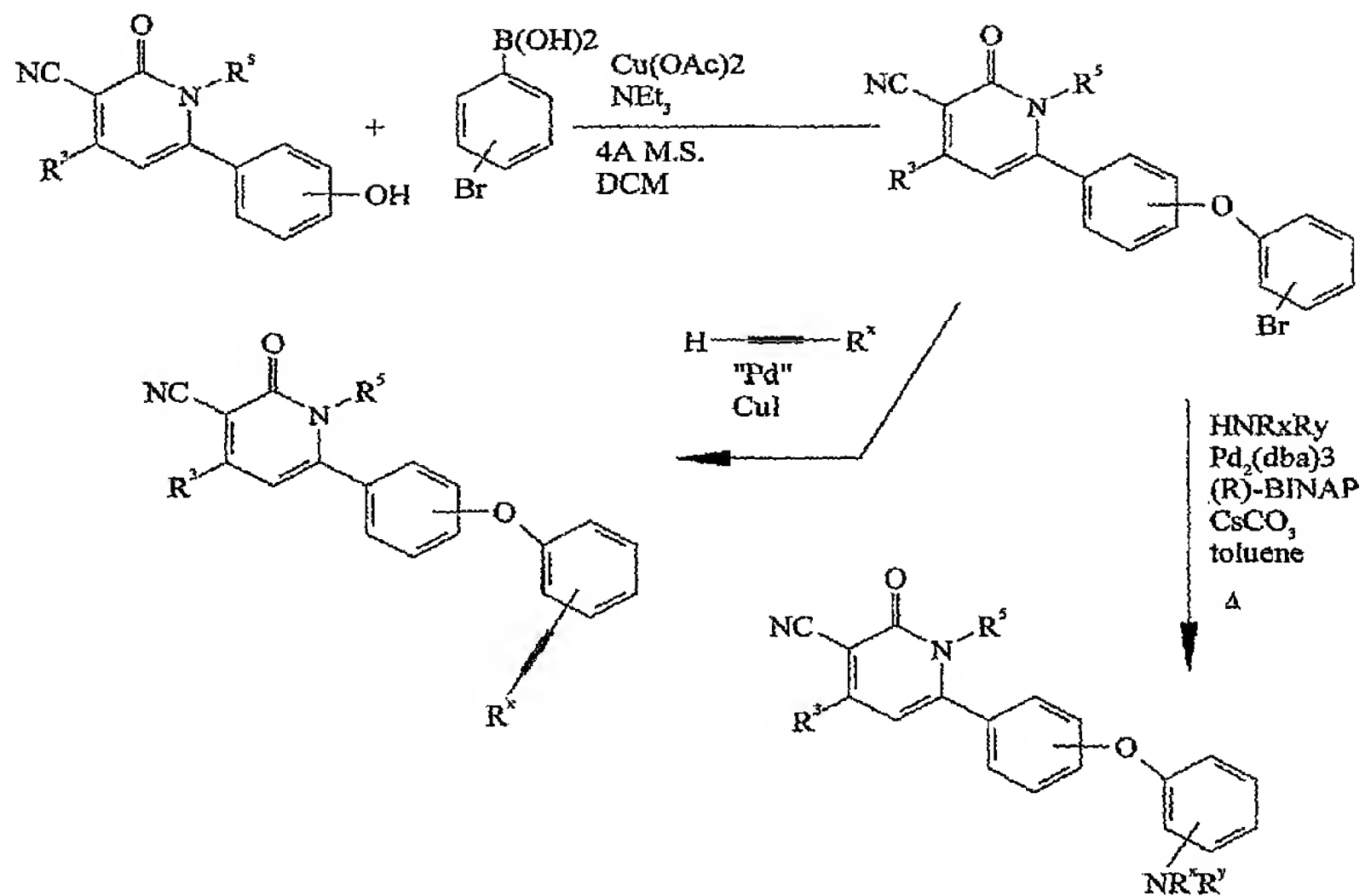


5

10

-99-

Scheme 13:



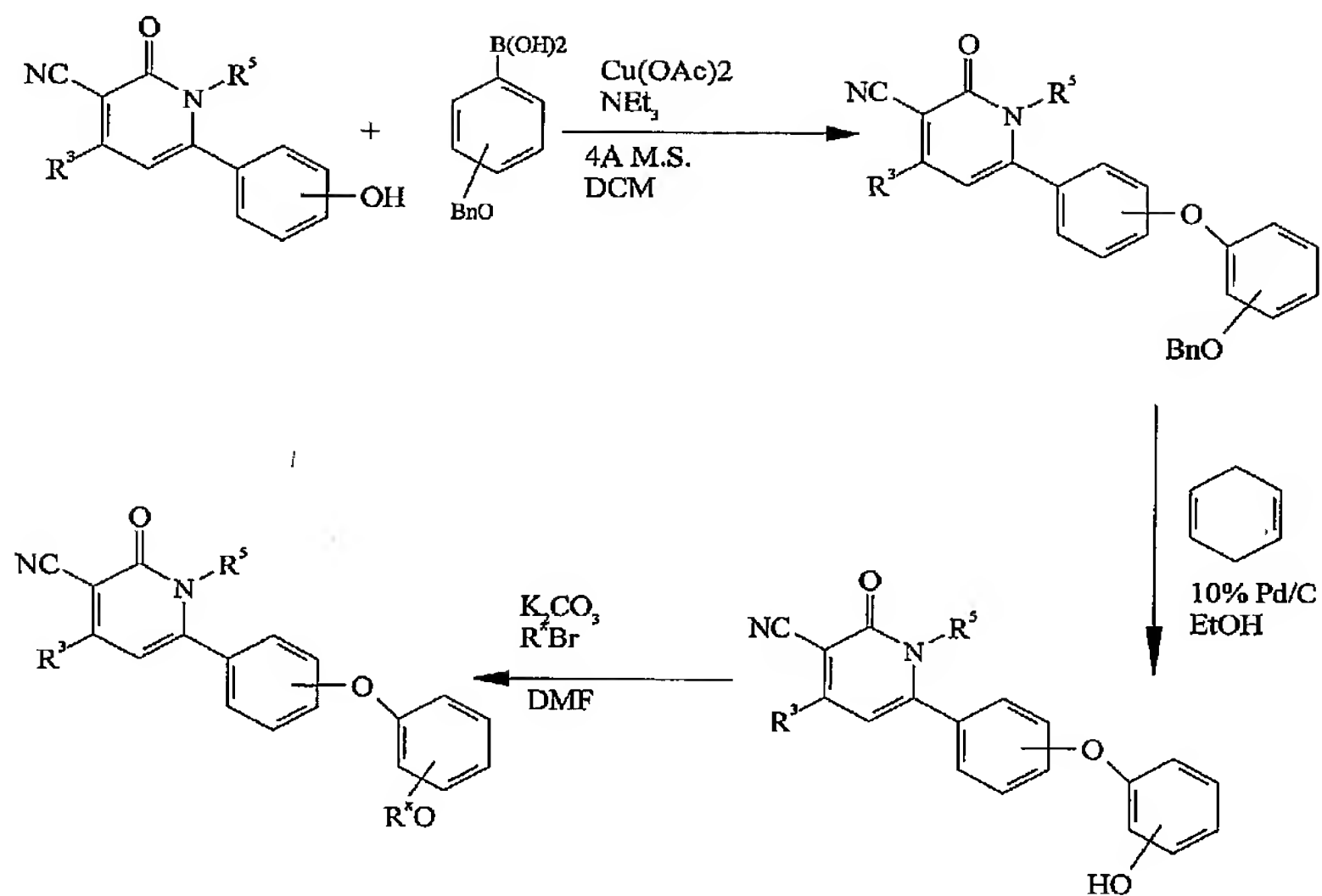
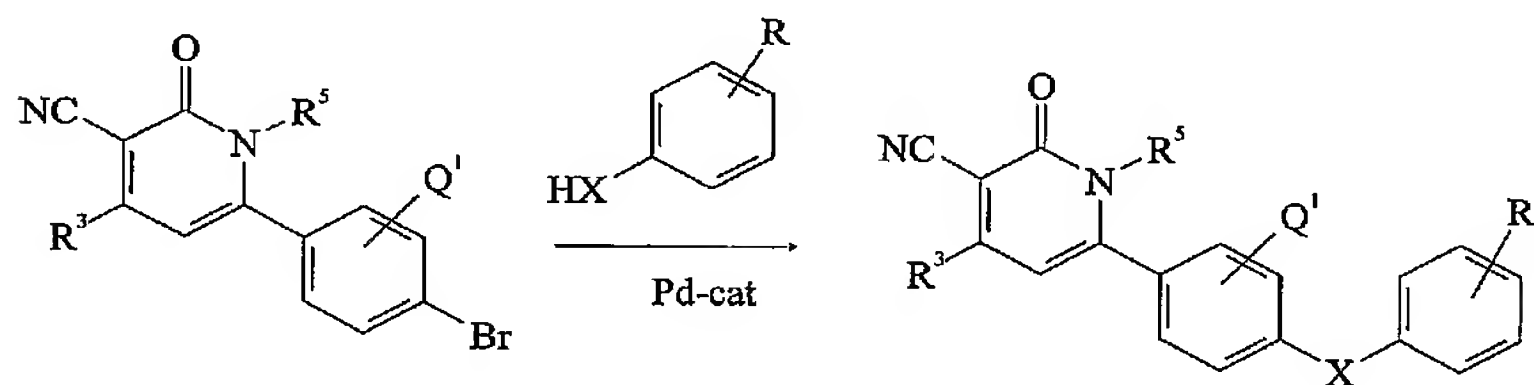
5

10

15

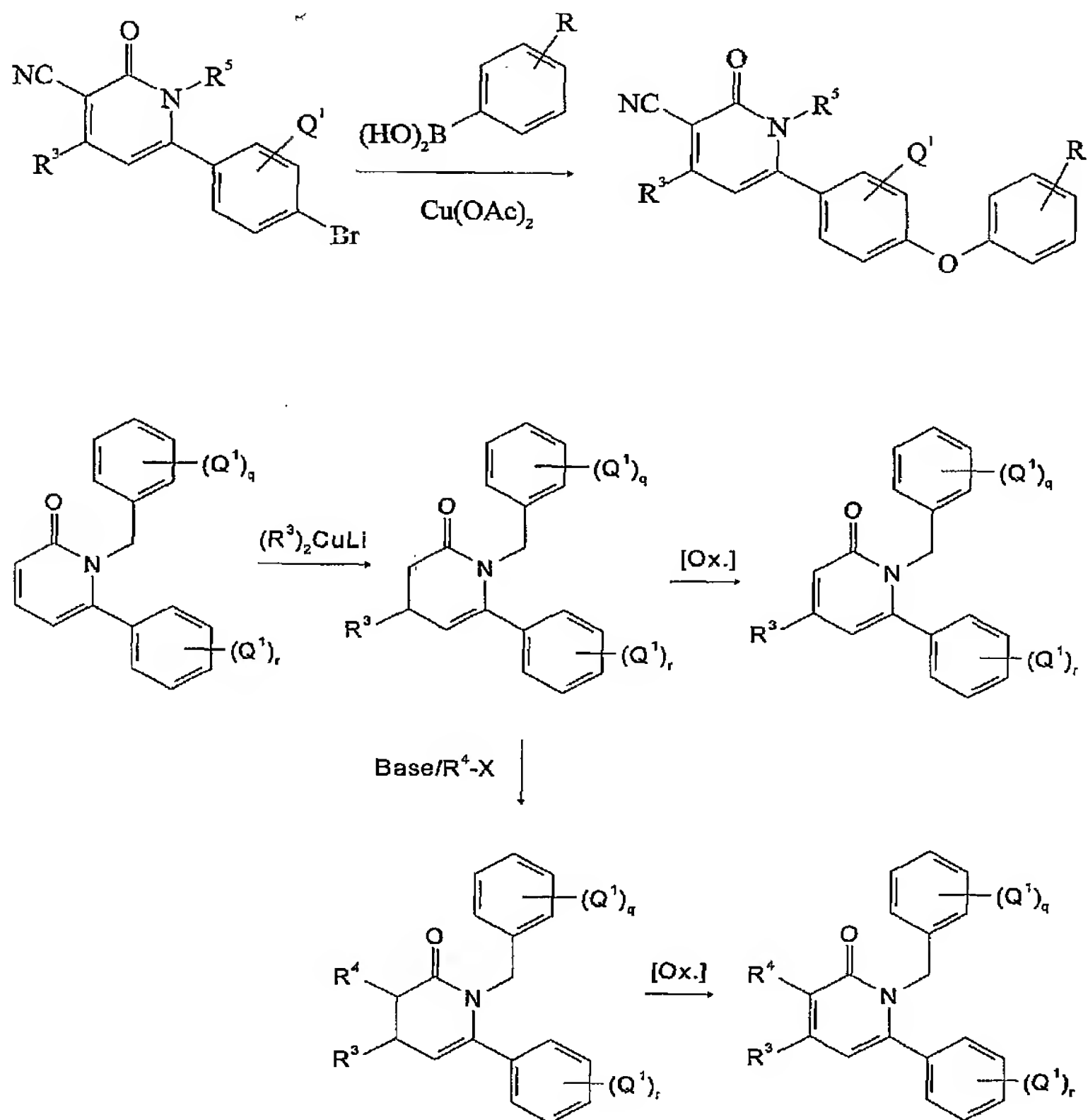
-100-

Scheme 14:

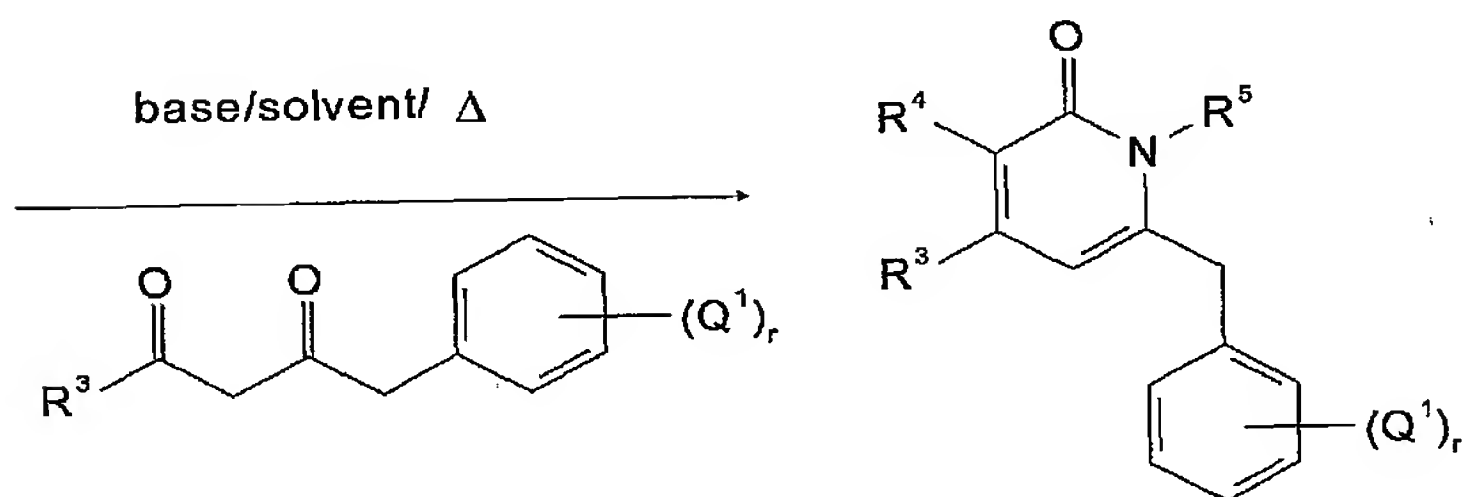
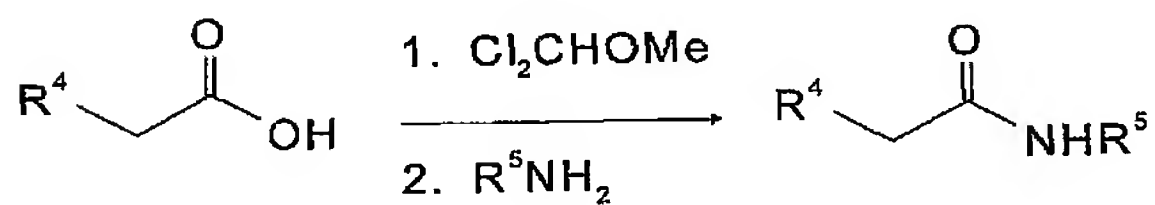
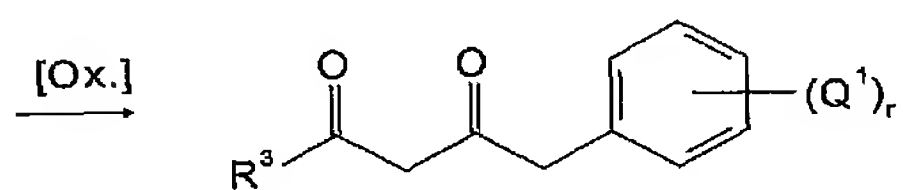
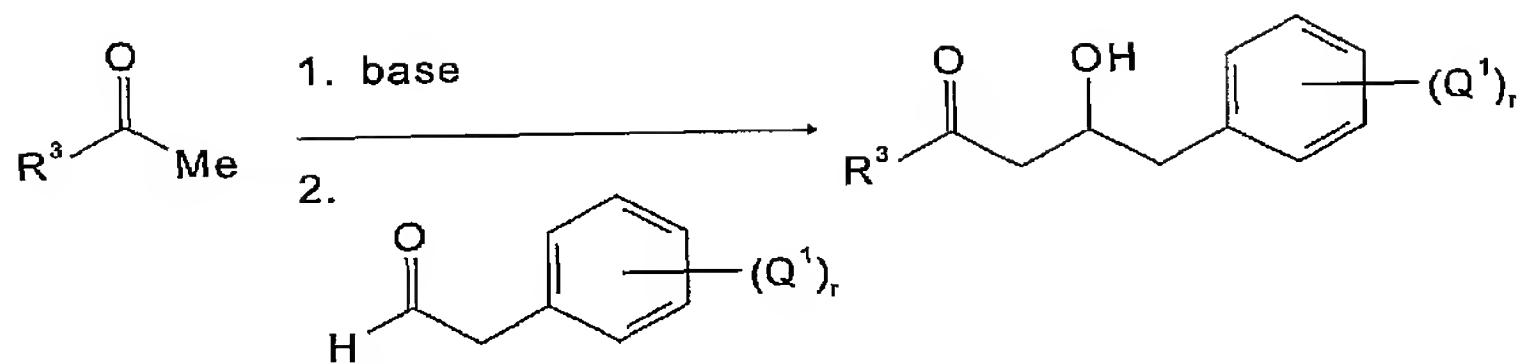
Scheme 15 (see, *e.g.*, Attila *et al.* (1999) *J. Am. Chem. Soc.* 121:4369-4378):

-101-

Scheme 16 (see, *e.g.*, Evans *et al.* (1998) *Tetrahedron Lett.* 39:2937-2940):



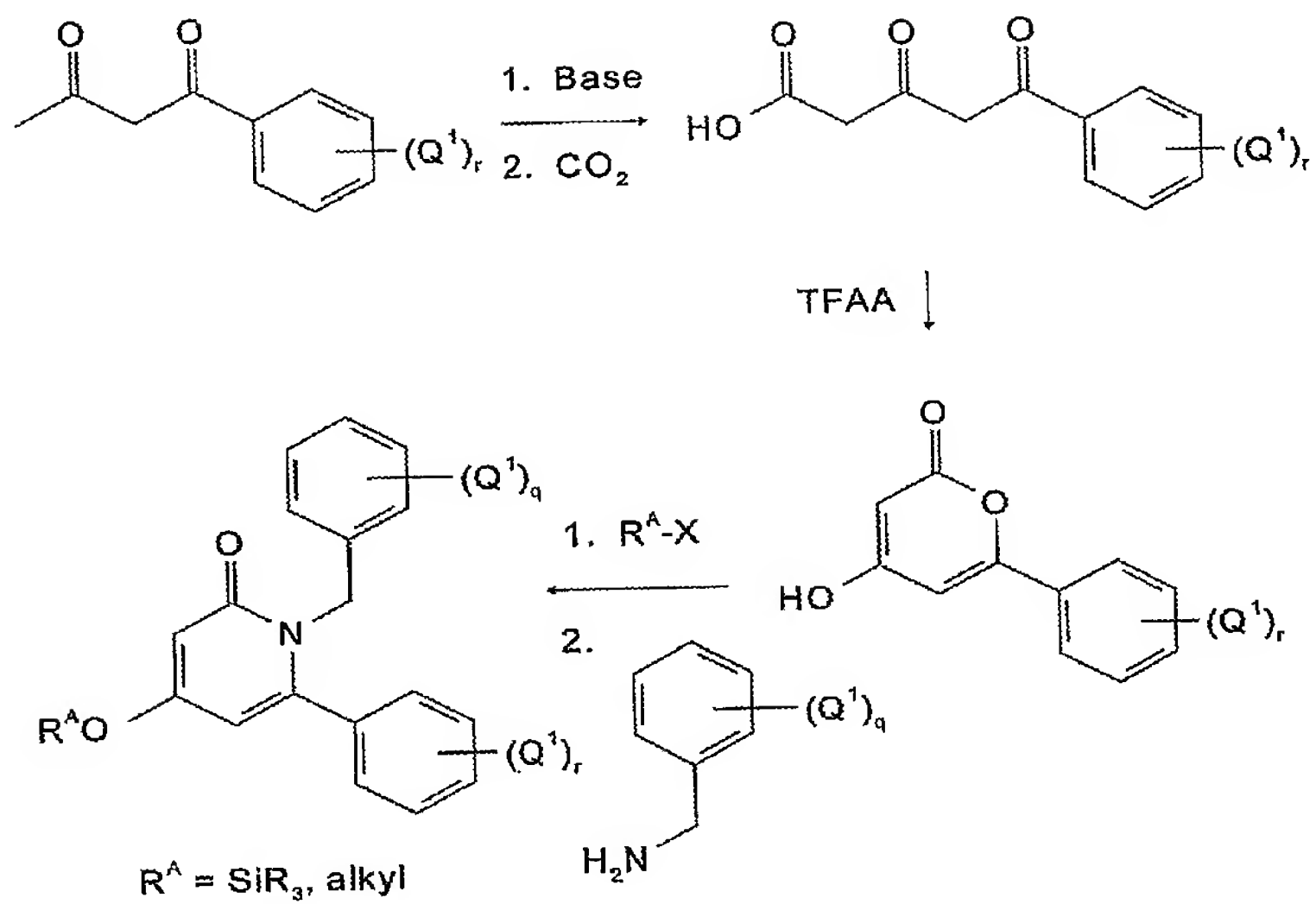
-102-



5

10

-103-



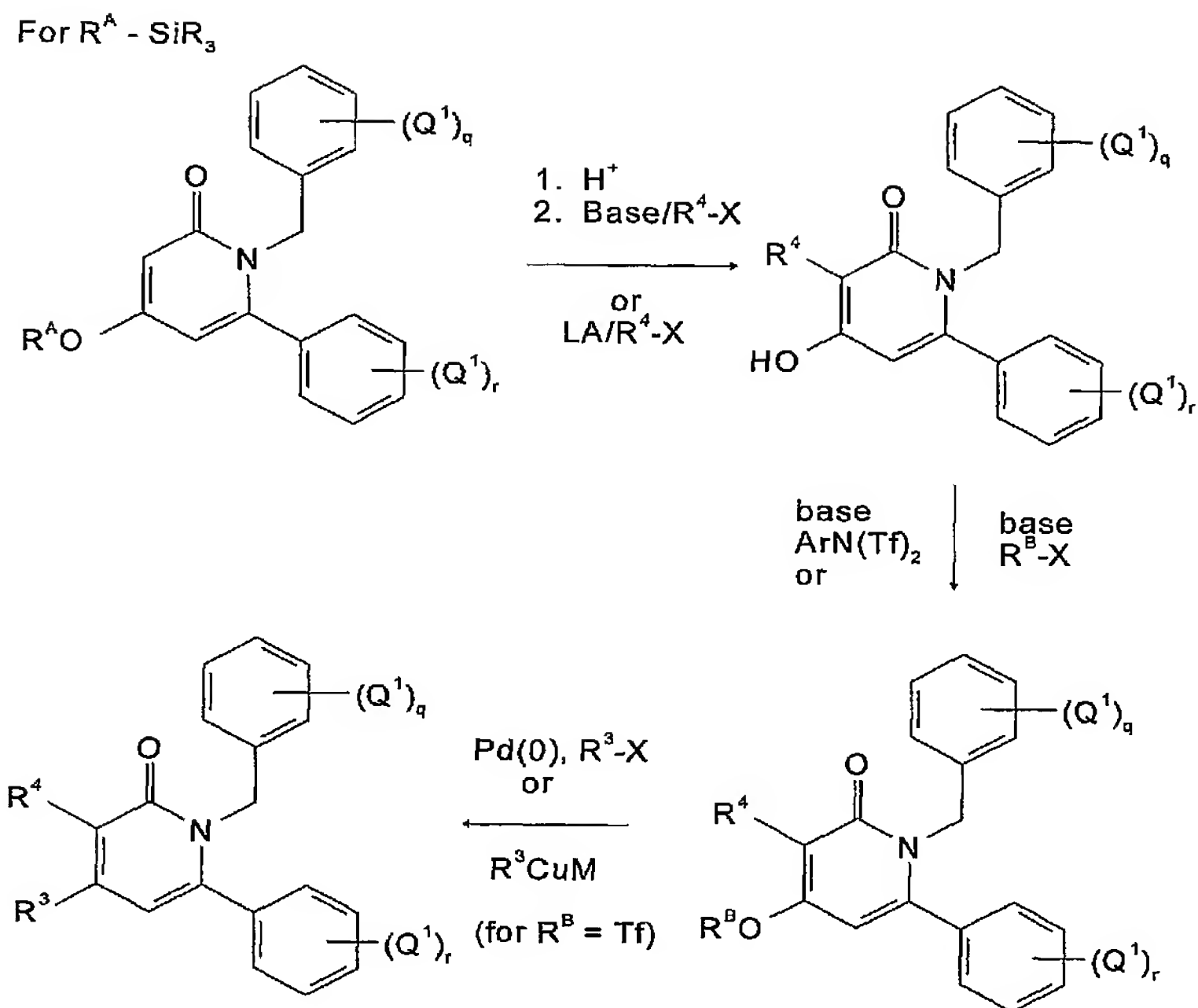
5

10

15

20

-104-



- Starting materials in the synthesis examples provided herein are either available from commercial sources or via literature procedures. All commercially available compounds were used without further purification unless otherwise indicated. $CDCl_3$ (99.8% D, Cambridge Isotope Laboratories) was used in all experiments as indicated. 1H NMR spectra were recorded on a Bruker Avance 400 MHz NMR spectrometer. Significant peaks are tabulated and typically include: number of protons, multiplicity (s, singlet; d, double; t, triplet; q, quartet; m, multiplet; br s, broad singlet) and coupling constant(s) in Hertz. Chemical shifts are reported as parts per million (δ) relative to tetramethylsilane. Mass spectra were recorded on a Perkin-Elmer SCIEX HPLC/MS instrument

-105-

using reverse-phase conditions (acetonitrile/water, 0.05% trifluoroacetic acid) and electrospray (ES) ionization. Abbreviations used in the examples below have their accepted meanings in the chemical literature. For example, CH₂Cl₂ (dichloromethane), C₆H₆ (benzene), TFA

5 (trifluoroacetic acid), EtOAc (Ethyl Acetate), Et₂O (diethyl ether), DMAP (4-dimethylaminopyridine), DMF (N,N-dimethylformamide) and THF (tetrahydrofuran). Flash chromatography was performed using Merck Silica Gel 60 (230-400 mesh).

D. Formulation of pharmaceutical compositions

10 The pharmaceutical compositions provided herein contain therapeutically effective amounts of one or more of the nuclear receptor activity modulators provided herein that are useful in the prevention, treatment, or amelioration of one or more of the symptoms of diseases or disorders associated with nuclear receptor activity, including LXR and/or

15 orphan nuclear receptor activity. Such diseases or disorders include, but are not limited to, hypercholesterolemia, hyperlipoproteinemia, hypertriglyceridemia, lipodystrophy, hyperglycemia, diabetes mellitus, dyslipidemia, atherosclerosis, gallstone disease, acne vulgaris, acneiform skin conditions, diabetes, Parkinson's disease, cancer, Alzheimer's

20 disease, inflammation, immunological disorders, lipid disorders, obesity, conditions characterized by a perturbed epidermal barrier function, conditions of disturbed differentiation or excess proliferation of the epidermis or mucous membrane, and cardiovascular disorders.

The compositions contain one or more compounds provided

25 herein. The compounds are preferably formulated into suitable pharmaceutical preparations such as solutions, suspensions, tablets, dispersible tablets, pills, capsules, powders, sustained release formulations or elixirs, for oral administration or in sterile solutions or suspensions for parenteral administration, as well as transdermal patch

-106-

preparation and dry powder inhalers. Typically the compounds described above are formulated into pharmaceutical compositions using techniques and procedures well known in the art (see, e.g., Ansel *Introduction to Pharmaceutical Dosage Forms, Fourth Edition 1985*, 126).

5 In the compositions, effective concentrations of one or more compounds or pharmaceutically acceptable derivatives is (are) mixed with a suitable pharmaceutical carrier or vehicle. The compounds may be derivatized as the corresponding salts, esters, enol ethers or esters, acids, bases, solvates, hydrates or prodrugs prior to formulation, as
10 described above. The concentrations of the compounds in the compositions are effective for delivery of an amount, upon administration, that treats, prevents, or ameliorates one or more of the symptoms of diseases or disorders associated with nuclear receptor activity or in which nuclear receptor activity is implicated. Such diseases
15 or disorders include, but are not limited to, hypercholesterolemia, hyperlipoproteinemia, hypertriglyceridemia, lipodystrophy, hyperglycemia, diabetes mellitus, dyslipidemia, atherosclerosis, gallstone disease, acne vulgaris, acneiform skin conditions, diabetes, Parkinson's disease, cancer, Alzheimer's disease, inflammation, immunological disorders, lipid
20 disorders, obesity, conditions characterized by a perturbed epidermal barrier function, conditions of disturbed differentiation or excess proliferation of the epidermis or mucous membrane, and cardiovascular disorders.

 Typically, the compositions are formulated for single dosage
25 administration. To formulate a composition, the weight fraction of compound is dissolved, suspended, dispersed or otherwise mixed in a selected vehicle at an effective concentration such that the treated condition is relieved or ameliorated. Pharmaceutical carriers or vehicles suitable for administration of the compounds provided herein include any

-107-

such carriers known to those skilled in the art to be suitable for the particular mode of administration.

In addition, the compounds may be formulated as the sole pharmaceutically active ingredient in the composition or may be
5 combined with other active ingredients. Liposomal suspensions, including tissue-targeted liposomes, such as tumor-targeted liposomes, may also be suitable as pharmaceutically acceptable carriers. These may be prepared according to methods known to those skilled in the art. For example, liposome formulations may be prepared as described in U.S.
10 Patent No. 4,522,811. Briefly, liposomes such as multilamellar vesicles (MLV's) may be formed by drying down egg phosphatidyl choline and brain phosphatidyl serine (7:3 molar ratio) on the inside of a flask. A solution of a compound provided herein in phosphate buffered saline lacking divalent cations (PBS) is added and the flask shaken until the lipid
15 film is dispersed. The resulting vesicles are washed to remove unencapsulated compound, pelleted by centrifugation, and then resuspended in PBS.

The active compound is included in the pharmaceutically acceptable carrier in an amount sufficient to exert a therapeutically useful
20 effect in the absence of undesirable side effects on the patient treated. The therapeutically effective concentration may be determined empirically by testing the compounds in *in vitro* and *in vivo* systems described herein and in International Patent Application Publication Nos. 99/27365 and 00/25134 (see, *e.g.*, EXAMPLES 13 and 14) and then extrapolated
25 therefrom for dosages for humans.

The concentration of active compound in the pharmaceutical composition will depend on absorption, inactivation and excretion rates of the active compound, the physicochemical characteristics of the compound, the dosage schedule, and amount administered as well as

-108-

other factors known to those of skill in the art. For example, the amount that is delivered is sufficient to ameliorate one or more of the symptoms of diseases or disorders associated with nuclear receptor activity or in which nuclear receptor activity is implicated, as described herein.

- 5 Typically a therapeutically effective dosage should produce a serum concentration of active ingredient of from about 0.1 ng/ml to about 50-100 μ g/ml. The pharmaceutical compositions typically should provide a dosage of from about 0.001 mg to about 2000 mg of compound per kilogram of body weight per day. Pharmaceutical dosage
- 10 unit forms are prepared to provide from about 1 mg to about 1000 mg and preferably from about 10 to about 500 mg of the essential active ingredient or a combination of essential ingredients per dosage unit form.

- The active ingredient may be administered at once, or may be divided into a number of smaller doses to be administered at intervals of
- 15 time. It is understood that the precise dosage and duration of treatment is a function of the disease being treated and may be determined empirically using known testing protocols or by extrapolation from *in vivo* or *in vitro* test data. It is to be noted that concentrations and dosage values may also vary with the severity of the condition to be alleviated.
- 20 It is to be further understood that for any particular subject, specific dosage regimens should be adjusted over time according to the individual need and the professional judgment of the person administering or supervising the administration of the compositions, and that the concentration ranges set forth herein are exemplary only and are not
- 25 intended to limit the scope or practice of the claimed compositions.

Pharmaceutically acceptable derivatives include acids, bases, enol ethers and esters, salts, esters, hydrates, solvates and prodrug forms. The derivative is selected such that its pharmacokinetic properties are superior to the corresponding neutral compound.

-109-

Thus, effective concentrations or amounts of one or more of the compounds described herein or pharmaceutically acceptable derivatives thereof are mixed with a suitable pharmaceutical carrier or vehicle for systemic, topical or local administration to form pharmaceutical
5 compositions. Compounds are included in an amount effective for ameliorating one or more symptoms of, or for treating or preventing diseases or disorders associated with nuclear receptor activity or in which nuclear receptor activity is implicated, as described herein. The concentration of active compound in the composition will depend on
10 absorption, inactivation, excretion rates of the active compound, the dosage schedule, amount administered, particular formulation as well as other factors known to those of skill in the art.

The compositions are intended to be administered by a suitable route, including orally, parenterally, rectally, topically and locally. For
15 oral administration, capsules and tablets are presently preferred. The compositions are in liquid, semi-liquid or solid form and are formulated in a manner suitable for each route of administration. Preferred modes of administration include parenteral and oral modes of administration. Oral administration is presently most preferred.

20 Solutions or suspensions used for parenteral, intradermal, subcutaneous, or topical application can include any of the following components: a sterile diluent, such as water for injection, saline solution, fixed oil, polyethylene glycol, glycerine, propylene glycol or other synthetic solvent; antimicrobial agents, such as benzyl alcohol and
25 methyl parabens; antioxidants, such as ascorbic acid and sodium bisulfite; chelating agents, such as ethylenediaminetetraacetic acid (EDTA); buffers, such as acetates, citrates and phosphates; and agents for the adjustment of tonicity such as sodium chloride or dextrose. Parenteral preparations can be enclosed in ampules, disposable syringes

-110-

or single or multiple dose vials made of glass, plastic or other suitable material.

In instances in which the compounds exhibit insufficient solubility, methods for solubilizing compounds may be used. Such methods are known to those of skill in this art, and include, but are not limited to, using cosolvents, such as dimethylsulfoxide (DMSO), using surfactants, such as TWEEN®, or dissolution in aqueous sodium bicarbonate. Derivatives of the compounds, such as prodrugs of the compounds may also be used in formulating effective pharmaceutical compositions.

10 Upon mixing or addition of the compound(s), the resulting mixture may be a solution, suspension, emulsion or the like. The form of the resulting mixture depends upon a number of factors, including the intended mode of administration and the solubility of the compound in the selected carrier or vehicle. The effective concentration is sufficient
15 for ameliorating the symptoms of the disease, disorder or condition treated and may be empirically determined.

The pharmaceutical compositions are provided for administration to humans and animals in unit dosage forms, such as tablets, capsules, pills, powders, granules, sterile parenteral solutions or suspensions, and
20 oral solutions or suspensions, and oil-water emulsions containing suitable quantities of the compounds or pharmaceutically acceptable derivatives thereof. The pharmaceutically therapeutically active compounds and derivatives thereof are typically formulated and administered in unit-dosage forms or multiple-dosage forms. Unit-dose forms as used
25 herein refers to physically discrete units suitable for human and animal subjects and packaged individually as is known in the art. Each unit-dose contains a predetermined quantity of the therapeutically active compound sufficient to produce the desired therapeutic effect, in association with the required pharmaceutical carrier, vehicle or diluent. Examples of

-111-

unit-dose forms include ampoules and syringes and individually packaged tablets or capsules. Unit-dose forms may be administered in fractions or multiples thereof. A multiple-dose form is a plurality of identical unit-dosage forms packaged in a single container to be administered in
5 segregated unit-dose form. Examples of multiple-dose forms include vials, bottles of tablets or capsules or bottles of pints or gallons. Hence, multiple dose form is a multiple of unit-doses which are not segregated in packaging.

The composition can contain along with the active ingredient: a
10 diluent such as lactose, sucrose, dicalcium phosphate, or carboxymethyl-cellulose; a lubricant, such as magnesium stearate, calcium stearate and talc; and a binder such as starch, natural gums, such as gum acacia-gelatin, glucose, molasses, polyvinylpyrrolidone, celluloses and derivatives thereof, povidone, crospovidones and other such binders known to those
15 of skill in the art. Liquid pharmaceutically administrable compositions can, for example, be prepared by dissolving, dispersing, or otherwise mixing an active compound as defined above and optional pharmaceutical adjuvants in a carrier, such as, for example, water, saline, aqueous dextrose, glycerol, glycols, ethanol, and the like, to thereby
20 form a solution or suspension. If desired, the pharmaceutical composition to be administered may also contain minor amounts of nontoxic auxiliary substances such as wetting agents, emulsifying agents, or solubilizing agents, pH buffering agents and the like, for example, acetate, sodium citrate, cyclodextrine derivatives, sorbitan monolaurate, triethanolamine
25 sodium acetate, triethanolamine oleate, and other such agents. Actual methods of preparing such dosage forms are known, or will be apparent, to those skilled in this art; for example, see Remington's Pharmaceutical Sciences, Mack Publishing Company, Easton, Pa., 15th Edition, 1975. The composition or formulation to be administered will, in any event,

-112-

contain a quantity of the active compound in an amount sufficient to alleviate the symptoms of the treated subject.

Dosage forms or compositions containing active ingredient in the range of 0.005% to 100% with the balance made up from non-toxic carrier may be prepared. For oral administration, a pharmaceutically acceptable non-toxic composition is formed by the incorporation of any of the normally employed excipients, such as, for example pharmaceutical grades of mannitol, lactose, starch, magnesium stearate, talcum, cellulose derivatives, sodium crosscarmellose, glucose, sucrose, magnesium carbonate or sodium saccharin. Such compositions include solutions, suspensions, tablets, capsules, powders and sustained release formulations, such as, but not limited to, implants and microencapsulated delivery systems, and biodegradable, biocompatible polymers, such as collagen, ethylene vinyl acetate, polyanhydrides, polyglycolic acid, polyorthoesters, polylactic acid and others. Methods for preparation of these compositions are known to those skilled in the art. The contemplated compositions may contain 0.001%-100% active ingredient, preferably 0.1-85%, typically 75-95%.

The active compounds or pharmaceutically acceptable derivatives may be prepared with carriers that protect the compound against rapid elimination from the body, such as time release formulations or coatings.

The compositions may include other active compounds to obtain desired combinations of properties. The compounds provided herein, or pharmaceutically acceptable derivatives thereof as described herein, may also be advantageously administered for therapeutic or prophylactic purposes together with another pharmacological agent known in the general art to be of value in treating one or more of the diseases or medical conditions referred to hereinabove, such as diseases or disorders associated with nuclear receptor activity or in which nuclear receptor

-113-

activity is implicated. It is to be understood that such combination therapy constitutes a further aspect of the compositions and methods of treatment provided herein.

1. Compositions for oral administration

5 Oral pharmaceutical dosage forms are either solid, gel or liquid. The solid dosage forms are tablets, capsules, granules, and bulk powders. Types of oral tablets include compressed, chewable lozenges and tablets which may be enteric-coated, sugar-coated or film-coated. Capsules may be hard or soft gelatin capsules, while granules and
10 powders may be provided in non-effervescent or effervescent form with the combination of other ingredients known to those skilled in the art.

In certain embodiments, the formulations are solid dosage forms, preferably capsules or tablets. The tablets, pills, capsules, troches and the like can contain any of the following ingredients, or compounds of a
15 similar nature: a binder; a diluent; a disintegrating agent; a lubricant; a glidant; a sweetening agent; and a flavoring agent.

Examples of binders include microcrystalline cellulose, gum tragacanth, glucose solution, acacia mucilage, gelatin solution, sucrose and starch paste. Lubricants include talc, starch, magnesium or calcium
20 stearate, lycopodium and stearic acid. Diluents include, for example, lactose, sucrose, starch, kaolin, salt, mannitol and dicalcium phosphate. Glidants include, but are not limited to, colloidal silicon dioxide. Disintegrating agents include crosscarmellose sodium, sodium starch glycolate, alginic acid, corn starch, potato starch, bentonite,
25 methylcellulose, agar and carboxymethylcellulose. Coloring agents include, for example, any of the approved certified water soluble FD and C dyes, mixtures thereof; and water insoluble FD and C dyes suspended on alumina hydrate. Sweetening agents include sucrose, lactose, mannitol and artificial sweetening agents such as saccharin, and any

-114-

number of spray dried flavors. Flavoring agents include natural flavors extracted from plants such as fruits and synthetic blends of compounds which produce a pleasant sensation, such as, but not limited to peppermint and methyl salicylate. Wetting agents include propylene glycol monostearate, sorbitan monooleate, diethylene glycol monolaurate and polyoxyethylene laural ether. Emetic-coatings include fatty acids, fats, waxes, shellac, ammoniated shellac and cellulose acetate phthalates. Film coatings include hydroxyethylcellulose, sodium carboxymethylcellulose, polyethylene glycol 4000 and cellulose acetate phthalate.

If oral administration is desired, the compound could be provided in a composition that protects it from the acidic environment of the stomach. For example, the composition can be formulated in an enteric coating that maintains its integrity in the stomach and releases the active compound in the intestine. The composition may also be formulated in combination with an antacid or other such ingredient.

When the dosage unit form is a capsule, it can contain, in addition to material of the above type, a liquid carrier such as a fatty oil. In addition, dosage unit forms can contain various other materials which modify the physical form of the dosage unit, for example, coatings of sugar and other enteric agents. The compounds can also be administered as a component of an elixir, suspension, syrup, wafer, sprinkle, chewing gum or the like. A syrup may contain, in addition to the active compounds, sucrose as a sweetening agent and certain preservatives, dyes and colorings and flavors.

The active materials can also be mixed with other active materials which do not impair the desired action, or with materials that supplement the desired action, such as antacids, H₂ blockers, and diuretics. The active ingredient is a compound or pharmaceutically acceptable derivative

-115-

thereof as described herein. Higher concentrations, up to about 98% by weight of the active ingredient may be included.

Pharmaceutically acceptable carriers included in tablets are binders, lubricants, diluents, disintegrating agents, coloring agents, 5 flavoring agents, and wetting agents. Enteric-coated tablets, because of the enteric-coating, resist the action of stomach acid and dissolve or disintegrate in the neutral or alkaline intestines. Sugar-coated tablets are compressed tablets to which different layers of pharmaceutically 10 acceptable substances are applied. Film-coated tablets are compressed tablets which have been coated with a polymer or other suitable coating. Multiple compressed tablets are compressed tablets made by more than one compression cycle utilizing the pharmaceutically acceptable substances previously mentioned. Coloring agents may also 15 be used in the above dosage forms. Flavoring and sweetening agents are used in compressed tablets, sugar-coated, multiple compressed and chewable tablets. Flavoring and sweetening agents are especially useful in the formation of chewable tablets and lozenges.

Liquid oral dosage forms include aqueous solutions, emulsions, 20 suspensions, solutions and/or suspensions reconstituted from non-effervescent granules and effervescent preparations reconstituted from effervescent granules. Aqueous solutions include, for example, elixirs and syrups. Emulsions are either oil-in-water or water-in-oil.

Elixirs are clear, sweetened, hydroalcoholic preparations. 25 Pharmaceutically acceptable carriers used in elixirs include solvents. Syrups are concentrated aqueous solutions of a sugar, for example, sucrose, and may contain a preservative. An emulsion is a two-phase system in which one liquid is dispersed in the form of small globules throughout another liquid. Pharmaceutically acceptable carriers used in

-116-

emulsions are non-aqueous liquids, emulsifying agents and preservatives. Suspensions use pharmaceutically acceptable suspending agents and preservatives. Pharmaceutically acceptable substances used in non-effervescent granules, to be reconstituted into a liquid oral dosage form, include diluents, sweeteners and wetting agents. Pharmaceutically acceptable substances used in effervescent granules, to be reconstituted into a liquid oral dosage form, include organic acids and a source of carbon dioxide. Coloring and flavoring agents are used in all of the above dosage forms.

10 Solvents include glycerin, sorbitol, ethyl alcohol and syrup. Examples of preservatives include glycerin, methyl and propylparaben, benzoic acid, sodium benzoate and alcohol. Examples of non-aqueous liquids utilized in emulsions include mineral oil and cottonseed oil. Examples of emulsifying agents include gelatin, acacia, tragacanth, bentonite, and surfactants such as polyoxyethylene sorbitan monooleate. 15 Suspending agents include sodium carboxymethylcellulose, pectin, tragacanth, Veegum and acacia. Diluents include lactose and sucrose. Sweetening agents include sucrose, syrups, glycerin and artificial sweetening agents such as saccharin. Wetting agents include propylene glycol monostearate, sorbitan monooleate, diethylene glycol monolaurate and polyoxyethylene lauryl ether. Organic acids include citric and tartaric acid. Sources of carbon dioxide include sodium bicarbonate and sodium carbonate. Coloring agents include any of the approved certified water soluble FD and C dyes, and mixtures thereof. Flavoring agents include 20 natural flavors extracted from plants such as fruits, and synthetic blends of compounds which produce a pleasant taste sensation.

For a solid dosage form, the solution or suspension, in for example propylene carbonate, vegetable oils or triglycerides, is preferably encapsulated in a gelatin capsule. Such solutions, and the preparation

-117-

and encapsulation thereof, are disclosed in U.S. Patent Nos 4,328,245; 4,409,239; and 4,410,545. For a liquid dosage form, the solution, *e.g.*, for example, in a polyethylene glycol, may be diluted with a sufficient quantity of a pharmaceutically acceptable liquid carrier, *e.g.*, water, to be
5 easily measured for administration.

Alternatively, liquid or semi-solid oral formulations may be prepared by dissolving or dispersing the active compound or salt in vegetable oils, glycols, triglycerides, propylene glycol esters (*e.g.*, propylene carbonate) and other such carriers, and encapsulating these
10 solutions or suspensions in hard or soft gelatin capsule shells. Other useful formulations include those set forth in U.S. Patent Nos. Re 28,819 and 4,358,603. Briefly, such formulations include, but are not limited to, those containing a compound provided herein, a dialkylated mono- or poly-alkylene glycol, including, but not limited to, 1,2-dimethoxymethane,
15 diglyme, triglyme, tetraglyme, polyethylene glycol-350-dimethyl ether, polyethylene glycol-550-dimethyl ether, polyethylene glycol-750-dimethyl ether wherein 350, 550 and 750 refer to the approximate average molecular weight of the polyethylene glycol, and one or more antioxidants, such as butylated hydroxytoluene (BHT), butylated
20 hydroxyanisole (BHA), propyl gallate, vitamin E, hydroquinone, hydroxycoumarins, ethanolamine, lecithin, cephalin, ascorbic acid, malic acid, sorbitol, phosphoric acid, thiodipropionic acid and its esters, and dithiocarbamates.

Other formulations include, but are not limited to, aqueous
25 alcoholic solutions including a pharmaceutically acceptable acetal. Alcohols used in these formulations are any pharmaceutically acceptable water-miscible solvents having one or more hydroxyl groups, including, but not limited to, propylene glycol and ethanol. Acetals include, but are

-118-

not limited to, di(lower alkyl) acetals of lower alkyl aldehydes such as acetaldehyde diethyl acetal.

In all embodiments, tablets and capsules formulations may be coated as known by those of skill in the art in order to modify or sustain
5 dissolution of the active ingredient. Thus, for example, they may be coated with a conventional enterically digestible coating, such as phenylsalicylate, waxes and cellulose acetate phthalate.

2. Injectables, solutions and emulsions

Parenteral administration, generally characterized by injection,
10 either subcutaneously, intramuscularly or intravenously is also contemplated herein. Injectables can be prepared in conventional forms, either as liquid solutions or suspensions, solid forms suitable for solution or suspension in liquid prior to injection, or as emulsions. Suitable excipients are, for example, water, saline, dextrose, glycerol or ethanol.
15 In addition, if desired, the pharmaceutical compositions to be administered may also contain minor amounts of non-toxic auxiliary substances such as wetting or emulsifying agents, pH buffering agents, stabilizers, solubility enhancers, and other such agents, such as for example, sodium acetate, sorbitan monolaurate, triethanolamine oleate
20 and cyclodextrins. Implantation of a slow-release or sustained-release system, such that a constant level of dosage is maintained (see, *e.g.*, U.S. Patent No. 3,710,795) is also contemplated herein. Briefly, a compound provided herein is dispersed in a solid inner matrix, *e.g.*, polymethylmethacrylate, polybutylmethacrylate, plasticized or
25 unplasticized polyvinylchloride, plasticized nylon, plasticized polyethyleneterephthalate, natural rubber, polyisoprene, polyisobutylene, polybutadiene, polyethylene, ethylene-vinylacetate copolymers, silicone rubbers, polydimethylsiloxanes, silicone carbonate copolymers, hydrophilic polymers such as hydrogels of esters of acrylic and

-119-

methacrylic acid, collagen, cross-linked polyvinylalcohol and cross-linked partially hydrolyzed polyvinyl acetate, that is surrounded by an outer polymeric membrane, *e.g.*, polyethylene, polyporpoylene, ethylene/propylene copolymers, ethylene/ethyl acrylate copolymers, 5 ethylene/vinylacetate copolymers, silicone rubbers, polydimethyl siloxanes, neoprene rubber, chlorinated polyethylene, polyvinylchloride, vinylchloride copolymers with vinyl acetate, vinylidene chloride, ethylene and propylene, ionomer polyethylene terephthalate, butyl rubber epichlorohydrin rubbers, ethylene/vinyl alcohol copolymer, ethylene/vinyl 10 acetate/vinyl alcohol terpolymer, and ethylene/vinyloxyethanol copolymer, that is insoluble in body fluids. The compound diffuses through the outer polymeric membrane in a release rate controlling step. The percentage of active compound contained in such parenteral compositions is highly dependent on the specific nature thereof, as well 15 as the activity of the compound and the needs of the subject.

Parenteral administration of the compositions includes intravenous, subcutaneous and intramuscular administrations. Preparations for parenteral administration include sterile solutions ready for injection, sterile dry soluble products, such as lyophilized powders, ready to be 20 combined with a solvent just prior to use, including hypodermic tablets, sterile suspensions ready for injection, sterile dry insoluble products ready to be combined with a vehicle just prior to use and sterile emulsions. The solutions may be either aqueous or nonaqueous.

If administered intravenously, suitable carriers include physiological 25 saline or phosphate buffered saline (PBS), and solutions containing thickening and solubilizing agents, such as glucose, polyethylene glycol, and polypropylene glycol and mixtures thereof.

-120-

Pharmaceutically acceptable carriers used in parenteral preparations include aqueous vehicles, nonaqueous vehicles, antimicrobial agents, isotonic agents, buffers, antioxidants, local anesthetics, suspending and dispersing agents, emulsifying agents, sequestering or chelating agents and other pharmaceutically acceptable substances.

Examples of aqueous vehicles include Sodium Chloride Injection, Ringers Injection, Isotonic Dextrose Injection, Sterile Water Injection, Dextrose and Lactated Ringers Injection. Nonaqueous parenteral vehicles include fixed oils of vegetable origin, cottonseed oil, corn oil, sesame oil and peanut oil. Antimicrobial agents in bacteriostatic or fungistatic concentrations must be added to parenteral preparations packaged in multiple-dose containers which include phenols or cresols, mercurials, benzyl alcohol, chlorobutanol, methyl and propyl p-hydroxybenzoic acid esters, thimerosal, benzalkonium chloride and benzethonium chloride. Isotonic agents include sodium chloride and dextrose. Buffers include phosphate and citrate. Antioxidants include sodium bisulfate. Local anesthetics include procaine hydrochloride. Suspending and dispersing agents include sodium carboxymethylcellulose, hydroxypropyl methylcellulose and polyvinylpyrrolidone. Emulsifying agents include Polysorbate 80 (TWEEN® 80). A sequestering or chelating agent of metal ions include EDTA. Pharmaceutical carriers also include ethyl alcohol, polyethylene glycol and propylene glycol for water miscible vehicles and sodium hydroxide, hydrochloric acid, citric acid or lactic acid for pH adjustment.

The concentration of the pharmaceutically active compound is adjusted so that an injection provides an effective amount to produce the desired pharmacological effect. The exact dose depends on the age, weight and condition of the patient or animal as is known in the art.

-121-

The unit-dose parenteral preparations are packaged in an ampoule, a vial or a syringe with a needle. All preparations for parenteral administration must be sterile, as is known and practiced in the art.

Illustratively, intravenous or intraarterial infusion of a sterile aqueous solution containing an active compound is an effective mode of administration. Another embodiment is a sterile aqueous or oily solution or suspension containing an active material injected as necessary to produce the desired pharmacological effect.

Injectables are designed for local and systemic administration. Typically a therapeutically effective dosage is formulated to contain a concentration of at least about 0.1% w/w up to about 90% w/w or more, preferably more than 1% w/w of the active compound to the treated tissue(s). The active ingredient may be administered at once, or may be divided into a number of smaller doses to be administered at intervals of time. It is understood that the precise dosage and duration of treatment is a function of the tissue being treated and may be determined empirically using known testing protocols or by extrapolation from *in vivo* or *in vitro* test data. It is to be noted that concentrations and dosage values may also vary with the age of the individual treated. It is to be further understood that for any particular subject, specific dosage regimens should be adjusted over time according to the individual need and the professional judgment of the person administering or supervising the administration of the formulations, and that the concentration ranges set forth herein are exemplary only and are not intended to limit the scope or practice of the claimed formulations.

The compound may be suspended in micronized or other suitable form or may be derivatized to produce a more soluble active product or to produce a prodrug. The form of the resulting mixture depends upon a number of factors, including the intended mode of administration and the

-122-

solubility of the compound in the selected carrier or vehicle. The effective concentration is sufficient for ameliorating the symptoms of the condition and may be empirically determined.

3. Lyophilized powders

5 Of interest herein are also lyophilized powders, which can be reconstituted for administration as solutions, emulsions and other mixtures. They may also be reconstituted and formulated as solids or gels.

The sterile, lyophilized powder is prepared by dissolving a
10 compound provided herein, or a pharmaceutically acceptable derivative thereof, in a suitable solvent. The solvent may contain an excipient which improves the stability or other pharmacological component of the powder or reconstituted solution, prepared from the powder. Excipients that may be used include, but are not limited to, dextrose, sorbital,
15 fructose, corn syrup, xylitol, glycerin, glucose, sucrose or other suitable agent. The solvent may also contain a buffer, such as citrate, sodium or potassium phosphate or other such buffer known to those of skill in the art at, typically, about neutral pH. Subsequent sterile filtration of the solution followed by lyophilization under standard conditions known to
20 those of skill in the art provides the desired formulation. Generally, the resulting solution will be apportioned into vials for lyophilization. Each vial will contain a single dosage (10-1000 mg, preferably 100-500 mg) or multiple dosages of the compound. The lyophilized powder can be stored under appropriate conditions, such as at about 4 °C to room
25 temperature.

Reconstitution of this lyophilized powder with water for injection provides a formulation for use in parenteral administration. For reconstitution, about 1-50 mg, preferably 5-35 mg, more preferably about 9-30 mg of lyophilized powder, is added per mL of sterile water or

-123-

other suitable carrier. The precise amount depends upon the selected compound. Such amount can be empirically determined.

4. Topical administration

Topical mixtures are prepared as described for the local and systemic administration. The resulting mixture may be a solution, suspension, emulsions or the like and are formulated as creams, gels, ointments, emulsions, solutions, elixirs, lotions, suspensions, tinctures, pastes, foams, aerosols, irrigations, sprays, suppositories, bandages, dermal patches or any other formulations suitable for topical administration.

The compounds or pharmaceutically acceptable derivatives thereof may be formulated as aerosols for topical application, such as by inhalation (see, *e.g.*, U.S. Patent Nos. 4,044,126, 4,414,209, and 4,364,923, which describe aerosols for delivery of a steroid useful for treatment of inflammatory diseases, particularly asthma). These formulations for administration to the respiratory tract can be in the form of an aerosol or solution for a nebulizer, or as a microfine powder for insufflation, alone or in combination with an inert carrier such as lactose. In such a case, the particles of the formulation will typically have diameters of less than 50 microns, preferably less than 10 microns.

The compounds may be formulated for local or topical application, such as for topical application to the skin and mucous membranes, such as in the eye, in the form of gels, creams, and lotions and for application to the eye or for intracisternal or intraspinal application. Topical administration is contemplated for transdermal delivery and also for administration to the eyes or mucosa, or for inhalation therapies. Nasal solutions of the active compound alone or in combination with other pharmaceutically acceptable excipients can also be administered.

-124-

These solutions, particularly those intended for ophthalmic use, may be formulated as 0.01% - 10% isotonic solutions, pH about 5-7, with appropriate salts.

5. Compositions for other routes of administration

5 Other routes of administration, such as topical application, transdermal patches, and rectal administration are also contemplated herein.

For example, pharmaceutical dosage forms for rectal administration are rectal suppositories, capsules and tablets for systemic effect. Rectal
10 suppositories are used herein mean solid bodies for insertion into the rectum which melt or soften at body temperature releasing one or more pharmacologically or therapeutically active ingredients. Pharmaceutically acceptable substances utilized in rectal suppositories are bases or vehicles and agents to raise the melting point. Examples of bases
15 include cocoa butter (theobroma oil), glycerin-gelatin, carbowax (polyoxyethylene glycol) and appropriate mixtures of mono-, di- and triglycerides of fatty acids. Combinations of the various bases may be used. Agents to raise the melting point of suppositories include spermaceti and wax. Rectal suppositories may be prepared either by the
20 compressed method or by molding. The typical weight of a rectal suppository is about 2 to 3 gm.

Tablets and capsules for rectal administration are manufactured using the same pharmaceutically acceptable substance and by the same methods as for formulations for oral administration.

25 6. Articles of manufacture

The compounds or pharmaceutically acceptable derivatives may be packaged as articles of manufacture containing

i) packaging material,

-125-

ii) a compound or pharmaceutically acceptable derivative thereof provided herein, which is effective for modulating the activity of nuclear receptors, including LXR and/or orphan nuclear receptors, or for treatment, prevention or amelioration of one or more symptoms of
5 nuclear receptor, including LXR and/or orphan nuclear receptor, mediated diseases or disorders, or diseases or disorders in which nuclear receptor activity, including LXR and/or orphan nuclear receptor activity is implicated, within the packaging material, and

iii) a label that indicates that the compound or composition, or
10 pharmaceutically acceptable derivative thereof, is used for modulating the activity of nuclear receptors, including LXR and/or orphan nuclear receptors, or for treatment, prevention or amelioration of one or more symptoms of nuclear receptor, including LXR and/or orphan nuclear
15 receptor, mediated diseases or disorders, or diseases or disorders in which nuclear receptor activity, including LXR and/or orphan nuclear receptor activity is implicated.

The articles of manufacture provided herein contain packaging materials. Packaging materials for use in packaging pharmaceutical products are well known to those of skill in the art. See, *e.g.*, U.S.
20 Patent Nos. 5,323,907, 5,052,558 and 5,033,252. Examples of pharmaceutical packaging materials include, but are not limited to, blister packs, bottles, tubes, inhalers, pumps, bags, vials, containers, syringes, bottles, and any packaging material suitable for a selected formulation and intended mode of administration and treatment. A wide array of
25 formulations of the compounds and compositions provided herein are contemplated as are a variety of treatments for any disease or disorder in which nuclear receptor activity, including LXR and/or orphan nuclear receptor activity, is implicated as a mediator or contributor to the symptoms or cause.

-126-

E. Evaluation of the Utility of the Compounds

Standard physiological, pharmacological and biochemical procedures are available for testing the compounds to identify those that possess biological activities that modulate the activity or nuclear
5 receptors, including the LXRs (LXR α and LXR β). Such assays include, for example, biochemical assays such as binding assays, fluorescence polarization assays, FRET based coactivator recruitment assays (see generally Glickman *et al.*, J. Biomolecular Screening, 7 No. 1 3-10 (2002), as well as cell based assays including the co-transfection assay,
10 the use of LBD-Gal 4 chimeras and protein-protein interaction assays, (see, Lehmann. *et al.*, J. Biol Chem., 272(6) 3137-3140 (1997).

High throughput screening systems are commercially available (see, e.g., Zymark Corp., Hopkinton, MA; Air Technical Industries, Mentor, OH; Beckman Instruments Inc., Fullerton, CA; Precision
15 Systems, Inc., Natick, MA) that enable these assays to be run in a high throughput mode. These systems typically automate entire procedures, including all sample and reagent pipetting, liquid dispensing timed incubations, and final readings of the microplate in detector(s) appropriate for the assay. These configurable systems provide high
20 throughput and rapid start up as well as a high degree of flexibility and customization. The manufacturers of such systems provide detailed protocols for various high throughput systems. Thus, for example, Zymark Corp. provides technical bulletins describing screening systems for detecting the modulation of gene transcription, ligand binding, and
25 the like.

Assays that do not require washing or liquid separation steps are preferred for such high throughput screening systems and include biochemical assays such as fluorescence polarization assays (see for example, Owicki, J., Biomol Screen 2000 Oct; 5(5):297) scintillation

-127-

proximity assays (SPA) (see for example, Carpenter *et al.*, Methods Mol Biol 2002; 190:31-49) and fluorescence resonance energy transfer (FRET) or time resolved FRET based coactivator recruitment assays (Mukherjee *et al.*, J Steroid Biochem Mol Biol 2002 Jul;81(3):217-25; 5 (Zhou *et al.*, Mol Endocrinol. 1998 Oct; 12(10):1594-604). Generally such assays can be preformed using either the full length receptor, or isolated ligand binding domain (LBD). In the case of LXR α the LBD comprises amino acids 188-447, for LXR β the LDB comprises amino acids 198-461, and for FXR, the LBD comprises amino acids 244 to 472 10 of the full length sequence.

If a fluorescently labeled ligand is available, fluorescence polarization assays provide a way of detecting binding of compounds to the nuclear receptor of interest by measuring changes in fluorescence polarization that occur as a result of the displacement of a trace amount 15 of the label ligand by the compound. Additionally this approach can also be used to monitor the ligand dependent association of a fluorescently labeled coactivator peptide to the nuclear receptor of interest to detect ligand binding to the nuclear receptor of interest.

The ability of a compound to bind to a receptor, or heterodimer 20 complex with RXR, can also be measured in a homogeneous assay format by assessing the degree to which the compound can compete off a radiolabelled ligand with known affinity for the receptor using a scintillation proximity assay (SPA). In this approach, the radioactivity emitted by a radiolabelled compound (for example, [3 H] 24,25 Epoxycholesterol) generates an optical signal when it is brought into close proximity to a scintillant such as a Ysi-copper containing bead, to which the nuclear receptor is bound. If the radiolabelled compound is displaced from the nuclear receptor the amount of light emitted from the nuclear receptor bound scintillant decreases, and this can be readily

-128-

detected using standard microplate liquid scintillation plate readers such as, for example, a Wallac MicroBeta reader.

The heterodimerization of LXR with RXR α can also be measured by fluorescence resonance energy transfer (FRET), or time resolved FRET, to
5 monitor the ability of the compounds provided herein to bind to LXR or other nuclear receptors. Both approaches rely upon the fact that energy transfer from a donor molecule to an acceptor molecule only occurs when donor and acceptor are in close proximity. Typically the purified LBD of the nuclear receptor of interest is labeled with biotin then mixed
10 with stoichiometric amounts of europium labeled streptavidin (Wallac Inc.), and the purified LBD of RXR α is labeled with a suitable fluorophore such as CY5™. Equimolar amounts of each modified LBD are mixed together and allowed to equilibrate for at least 1 hour prior to addition to either variable or constant concentrations of the sample for which the
15 affinity is to be determined. After equilibration, the time-resolved fluorescent signal is quantitated using a fluorescent plate reader. The affinity of the compound can then be estimated from a plot of fluorescence versus concentration of compound added.

This approach can also be exploited to measure the ligand
20 dependent interaction of a co-activator peptide with a nuclear receptor in order to characterize the agonist or antagonist activity of the compounds disclosed herein. Typically the assay in this case involves the use a recombinant Glutathione-S-transferase (GST)-nuclear receptor ligand binding domain (LBD) fusion protein and a synthetic biotinylated peptide
25 sequence derived from the receptor interacting domain of a co-activator peptide such as the steroid receptor coactivator 1 (SRC-1). Typically GST-LBD is labeled with a europium chelate (donor) via a europium-tagged anti-GST antibody, and the coactivator peptide is labeled with allophycocyanin via a streptavidin-biotin linkage.

-129-

In the presence of an agonist for the nuclear receptor, the peptide is recruited to the GST-LBD bringing europium and allophycocyanin into close proximity to enable energy transfer from the europium chelate to the allophycocyanin. Upon excitation of the complex with light at 340 nm excitation energy absorbed by the europium chelate is transmitted to the allophycocyanin moiety resulting in emission at 665 nm. If the europium chelate is not brought into close proximity to the allophycocyanin moiety there is little or no energy transfer and excitation of the europium chelate results in emission at 615 nm. Thus the intensity of light emitted at 665 nm gives an indication of the strength of the protein-protein interaction. The activity of a nuclear receptor antagonist can be measured by determining the ability of a compound to competitively inhibit (*i.e.*, IC_{50}) the activity of an agonist for the nuclear receptor.

In addition a variety of cell based assay methodologies may be successfully used in screening assays to identify and profile the specificity of compounds claimed herein. These approaches include the co-transfection assay, translocation assays, complementation assays and the use of gene activation technologies to over express endogenous nuclear receptors.

Three basic variants of the co-transfection assay strategy exist, co-transfection assays using full-length nuclear receptor, co transfection assays using chimeric nuclear receptors comprising the ligand binding domain of the nuclear receptor of interest fused to a heterologous DNA binding domain, and assays based around the use of the mammalian two hybrid assay system.

The basic co-transfection assay is based on the co-transfection into the cell of an expression plasmid to express the nuclear receptor of interest in the cell with a reporter plasmid comprising a reporter gene

-130-

whose expression is under the control of DNA sequence that is capable of interacting with that nuclear receptor. (See for example US Patents Nos. 5,071,773; 5,298,429 and 6,416,957). Treatment of the transfected cells with an agonist for the nuclear receptor increases the transcriptional activity of that receptor which is reflected by an increase in expression of the reporter gene, which may be measured by a variety of standard procedures.

For those receptors that function as heterodimers with RXR, such as the LXRs, the co-transfection assay typically includes the use of expression plasmids for both the nuclear receptor of interest and RXR. Typical co-transfection assays require access to the full length nuclear receptor and suitable response elements that provide sufficient screening sensitivity and specificity to the nuclear receptor of interest.

Genes encoding the following full-length previously described proteins, which are suitable for use in the co-transfection studies and profiling the compounds described herein, include human LXR α (SEQ ID 1), human LXR β (SEQ ID 3), rat FXR (SEQ ID 5), human FXR (SEQ ID 7), human RXR α (SEQ ID 9), human RXR β (SEQ ID 17), human RXR γ (SEQ ID 15), human PPAR α (SEQ ID 11) and human PPAR δ (SEQ ID 13). All accession numbers in this application refer to GenBank accession numbers.

Reporter plasmids may be constructed using standard molecular biological techniques by placing cDNA encoding for the reporter gene downstream from a suitable minimal promoter. For example luciferase reporter plasmids may be constructed by placing cDNA encoding firefly luciferase immediately down stream from the herpes virus thymidine kinase promoter (located at nucleotides residues-105 to +51 of the thymidine kinase nucleotide sequence) which is linked in turn to the various response elements.

-131-

Numerous methods of co-transfecting the expression and reporter plasmids are known to those of skill in the art and may be used for the co-transfection assay to introduce the plasmids into a suitable cell type. Typically such a cell will not endogenously express nuclear receptors that
5 interact with the response elements used in the reporter plasmid.

Numerous reporter gene systems are known in the art and include, for example, alkaline phosphatase Berger, J., *et al.* (1988) *Gene* **66** 1-10; Kain, S.R. (1997) *Methods. Mol. Biol.* **63** 49-60), β -galactosidase (See, U.S. Patent No. 5,070,012, issued Dec, 3, 1991 to Nolan *et al.*, and
10 Bronstein, I., *et al.*, (1989) *J. Chemilum. Biolum.* **4** 99-111), chloramphenicol acetyltransferase (See Gorman *et al.*, *Mol Cell Biol.* (1982) **2** 1044-51), β -glucuronidase, peroxidase, β -lactamase (U.S. Patent Nos. 5,741,657 and 5,955,604), catalytic antibodies, luciferases (U.S. Patents 5,221,623; 5,683,888; 5,674,713; 5,650,289;
15 5,843,746) and naturally fluorescent proteins (Tsien, R.Y. (1998) *Annu. Rev. Biochem.* **67** 509-44).

The use of chimeras comprising the ligand binding domain (LBD) of the nuclear receptor of interest fused to a heterologous DNA binding domain (DBD) expands the versatility of cell based assays by directing
20 activation of the nuclear receptor in question to defined DNA binding elements recognized by defined DNA binding domain (see WO95/18380). This assay expands the utility of cell based co-transfection assays in cases where the biological response or screening window using the native DNA binding domain is not satisfactory.

25 In general the methodology is similar to that used with the basic co-transfection assay, except that a chimeric construct is used in place of the full length nuclear receptor. As with the full length nuclear receptor, treatment of the transfected cells with an agonist for the nuclear receptor LBD increases the transcriptional activity of the

-132-

heterologous DNA binding domain which is reflected by an increase in expression of the reporter gene as described above. Typically for such chimeric constructs, the DNA binding domains from defined nuclear receptors, or from yeast or bacterially derived transcriptional regulators
5 such as members of the GAL 4 and Lex A/Umod super families are used.

A third cell based assay of utility for screening compounds claimed herein is a mammalian two-hybrid assay that measures the ability of the nuclear hormone receptor to interact with a cofactor in the presence of a ligand. (See for example, US Patent Nos. US 5,667,973, 5,283,173 and
10 5,468,614). The basic approach is to create three plasmid constructs that enable the interaction of the nuclear receptor with the interacting protein to be coupled to a transcriptional readout within a living cell. The first construct is an expression plasmid for expressing a fusion protein comprising the interacting protein, or a portion of that protein containing
15 the interacting domain, fused to a GAL4 DNA binding domain. The second expression plasmid comprises DNA encoding the nuclear receptor of interest fused to a strong transcription activation domain such as VP16, and the third construct comprises the reporter plasmid comprising a reporter gene with a minimal promoter and GAL4 upstream activating
20 sequences.

Once all three plasmids are introduced into a cell, the GAL4 DNA binding domain encoded in the first construct allows for specific binding of the fusion protein to GAL4 sites upstream of a minimal promoter. However because the GAL4 DNA binding domain typically has no strong
25 transcriptional activation properties in isolation, expression of the reporter gene occurs only at a low level. In the presence of a ligand, the nuclear receptor-VP16 fusion protein can bind to the GAL4-interacting protein fusion protein bringing the strong transcriptional activator VP16 in close proximity to the GAL4 binding sites and minimal promoter region of the

-133-

reporter gene. This interaction significantly enhances the transcription of the reporter gene, which can be measured for various reporter genes as described above. Transcription of the reporter gene is thus driven by the interaction of the interacting protein and nuclear receptor of interest in a
5 ligand dependent fashion.

Any compound which is a candidate for activation of LXR α or LXR β may be tested by these methods. Generally, compounds are tested at several different concentrations to optimize the chances that activation of the receptor will be detected and recognized if present. Typically
10 assays are performed in triplicate and vary within experimental error by less than 15%. Each experiment is typically repeated three or more times with similar results.

Activity of the reporter gene can be conveniently normalized to the internal control and the data plotted as fold activation relative to
15 untreated cells. A positive control compound (agonist) may be included along with DMSO as high and low controls for normalization of the assay data. Similarly, antagonist activity can be measured by determining the ability of a compound to competitively inhibit the activity of an agonist.

Additionally the compounds and compositions can be evaluated for
20 their ability to increase or decrease the expression of genes known to be modulated by LXR α or β and other nuclear receptors in *vivo*, using Northern-blot, RT PCR or oligonucleotide microarray analysis to analyze RNA levels. Western-blot analysis can be used to measure expression of proteins encoded by LXR target genes. Genes that are known to be
25 regulated by the LXRs include the ATP binding cassette transporters ABCA1, ABCG1, ABCG5, ABCG8, the sterol response element binding protein 1c (SREBP1c) gene, stearoyl CoA desaturase 1 (SCD-1) and the apolipoprotein apoE gene (ApoE).

-134-

Established animal models exist for a number of diseases of direct relevance to the claimed compounds and these can be used to further profile and characterize the claimed compounds. These model systems include diabetic dislipidemia using Zucker (fa/fa) rats or (db/db) mice, spontaneous hyperlipidemia using apolipoprotein E deficient mice (ApoE^{-/-}), diet-induced hyperlipidemia, using low density lipoprotein receptor deficient mice (LDLR^{-/-}) and atherosclerosis using both the Apo E^{-/-} and LDL^{-/-} mice fed a western diet. (21% fat, 0.05% cholesterol). Additionally LXR or FXR animal models (e.g., knockout mice) can be used to further evaluate the present compounds and compositions *in vivo* (see, for example, Peet, *et al.*, *Cell*, 93:693-704 (1998), Sinal, *et al.*, *Cell*, 102: 731-744 (2000)).

F. Methods of Use of the compounds and compositions

Methods and compounds for selectively regulating LXR α or LXR β are also provided. In one embodiment, such compounds exhibit at least a 10 fold difference in IC₅₀, or EC₅₀ for LXR α compared to LXR β .

F. Methods of use of the compounds and compositions

Methods of use of the compounds and compositions provided herein are also provided. The methods involve both *in vitro* and *in vivo* uses of the compounds and compositions for altering nuclear receptor activity, including LXR and/or orphan nuclear receptor activity, and for treatment, prevention, or amelioration of one or more symptoms of diseases or disorder that are modulated by nuclear receptor activity, including LXR and/or orphan nuclear receptor activity, or in which nuclear receptor activity, including LXR and/or orphan nuclear receptor activity, is implicated.

Methods of reducing cholesterol levels and of modulating cholesterol metabolism are provided. As described above, LXR is

-135-

implicated in modulated cholesterol metabolism and catabolism. See, *e.g.*, International Patent Application Publication No. 00/40965.

Method of altering nuclear receptor activity, including liver X receptor (LXR) and/or orphan nuclear receptor activity, by contacting the
5 receptor with one or more compounds or compositions provided herein, are provided.

Methods of treatment, prevention, or amelioration of one or more symptoms of a disease or disorder which is affected by cholesterol, triglyceride, or bile acid levels are provided.

10 Methods of treatment, prevention, or amelioration of one or more symptoms of hypercholesterolemia (see, *e.g.*, International Patent Application Publication No. WO 00/57915); hyperlipoproteinemia (see, *e.g.*, International Patent Application Publication No. WO 01/60818);
hypertriglyceridemia, lipodystrophy, hyperglycemia or diabetes mellitus
15 (see, *e.g.*, International Patent Application Publication No. WO 01/82917); dyslipidemia, obesity, atherosclerosis, lipid disorders, cardiovascular disorders, or gallstone disease (see, *e.g.*, International Patent Application Publication No. WO 00/37077); acne vulgaris or
acneiform skin conditions (see, *e.g.*, International Patent Application
20 Publication No. WO 00/49992); atherosclerosis, diabetes, Parkinson's disease, inflammation, immunological disorders, obesity, cancer or Alzheimer's disease (see, *e.g.*, International Patent Application Publication No. WO 00/17334); conditions characterized by a perturbed
epidermal barrier function or conditions of disturbed differentiation or
25 excess proliferation of the epidermis or mucous membrane (see, *e.g.*, U.S. Patent Nos. 6,184,215 and 6,187,814, and International Patent Application Publication No. Wo 98/32444) are provided.

Methods of increasing cholesterol efflux from mammalian cells using the compounds and compositions provided herein are provided

-136-

(see, *e.g.*, International Patent Application Publication No. WO 00/78972).

Methods of increasing the expression of ATP-Binding Cassette (ABC1) in mammalian cells using the compounds and compositions provided herein are provided (see, *e.g.*, International Patent Application Publication No. WO 00/78972).

Methods of treating, preventing, or ameliorating one or more symptoms of hypocholesterolemia using the compounds and compositions provided herein are also provided.

Methods of post-myocardial infarction therapy using the compounds and compositions provided herein are also provided (see, *e.g.*, International Patent Application Publication No. WO 01/03705).

Methods and compounds for selectively regulating LXR α or LXR β are also provided. In one embodiment, such compounds exhibit at least a 10 fold difference in IC_{50} , or EC_{50} for LXR α compared to LXR β .

G. Combination Therapy

Also contemplated herein is combination therapy using a compound provided herein, or a pharmaceutically acceptable derivative thereof, in combination with one or more of the following:

antihyperlipidemic agents, plasma HDL-raising agents, antihypercholesterolemic agents, cholesterol biosynthesis inhibitors (such as HMG CoA reductase inhibitors, such as lovastatin, simvastatin, pravastatin, fluvastatin, atorvastatin and rivastatin), acyl-coenzyme A:cholesterol acyltransferase (ACAT) inhibitors, probucol, raloxifene, nicotinic acid, niacinamide, cholesterol absorption inhibitors, bile acid sequestrants (such as anion exchange resins, or quaternary amines (*e.g.*, cholestyramine or colestipol)), low density lipoprotein receptor inducers, clofibrate, fenofibrate, benzofibrate, cipofibrate, gemfibrizol, vitamin B₆, vitamin B₁₂, anti-oxidant vitamins, β -blockers, anti-diabetes agents,

-137-

angiotensin II antagonists, angiotensin converting enzyme inhibitors, platelet aggregation inhibitors, fibrinogen receptor antagonists, aspirin or fibric acid derivatives. The compound provided herein, or pharmaceutically acceptable derivative thereof, is administered

- 5 simultaneously with, prior to, or after administration of one or more of the above agents. Pharmaceutical compositions containing a compound provided herein and one or more of the above agents are also provided.

- Combination therapy includes administration of a single pharmaceutical dosage formulation which contains a LXR selective
- 10 compound and one or more additional active agents, as well as administration of the LXR selective compound and each active agent in its own separate pharmaceutical dosage formulation. For example, a LXR agonist or antagonist claimed herein and an HMG-CoA reductase inhibitor can be administered to the patient together in a single oral
- 15 dosage composition such as a tablet or capsule, or each agent administered in separate oral dosage formulations. Where separate dosage formulations are used, the compounds described herein and one or more additional active agents can be administered at essentially the same time, *i.e.*, concurrently, or at separately staggered times, *i.e.*,
- 20 sequentially; combination therapy is understood to include all these regimens.

- The compound is, in one embodiment, administered with a cholesterol biosynthesis inhibitor, particularly an HMG-CoA reductase inhibitor. The term HMG-CoA reductase inhibitor is intended to include
- 25 all pharmaceutically acceptable salts, esters, free acids and lactone forms of compounds which have HMG-CoA reductase inhibitory activity and, therefore, the use of such salts, esters, free acids and lactone forms is included within the scope the compounds claimed herein. Compounds which have inhibitory activity for HMG-CoA reductase can be readily

-138-

identified using assays well-known in the art. For instance, suitable assays are described or disclosed in U.S. Patent No. 4,231,938 and WO 84/02131. Examples of suitable HMG-CoA reductase inhibitors include, but are not limited to, lovastatin (MEVACOR®; *see*, U.S. Patent No.

5 4,231,938); simvastatin (ZOCOR®; *see*, U.S. Patent No. 4,444,784); pravastatin sodium (PRAVACHOL®; *see*, U.S. Patent No. 4,346,227); fluvastatin sodium (LESCOL®; *see*, U.S. Patent No. 5,354,772); atorvastatin calcium (LIPITOR®; *see*, U.S. Patent No. 5,273,995) and rivastatin (also known as cerivastatin; *see*, U.S. Patent No. 5,177,080).

10 The structural formulas of these and additional HMG-CoA reductase inhibitors that can be used in the methods claimed herein are described at page 87 of M. Yalpani, "Cholesterol Lowering Drugs," *Chemistry & Industry*, pp. 85-89 (5 February 1996). In one embodiment, the HMG-CoA reductase inhibitor is selected from lovastatin and simvastatin.

15 Dosage information for HMG-CoA reductase inhibitors is well known in the art, since several HMG-CoA reductase inhibitors are marketed in the U.S. In particular, the daily dosage amounts of the HMG-CoA reductase inhibitor may be the same or similar to those amounts which are employed for anti-hypercholesterolemic treatment and
20 which are described in the *Physicians' Desk Reference* (PDR). For example, *see* the 50th Ed. of the PDR, 1996 (Medical Economics Co); in particular, *see* at page 216 the heading "Hypolipidemics," sub-heading "HMG-CoA Reductase Inhibitors," and the reference pages cited therein. In one embodiment, the oral dosage amount of HMG-CoA reductase
25 inhibitor is from about 1 to 200 mg/day and, in another embodiment, from about 5 to 160 mg/day. However, dosage amounts will vary depending on the potency of the specific HMG-CoA reductase inhibitor used as well as other factors as noted above. An HMG-CoA reductase

-139-

inhibitor which has sufficiently greater potency may be given in sub-milligram daily dosages.

As examples, the daily dosage amount for simvastatin may be selected from 5 mg, 10 mg, 20 mg, 40 mg, 80 mg and 160 mg; for
5 lovastatin, 10 mg, 20 mg, 40 mg and 80 mg; for fluvastatin sodium, 20 mg, 40 mg and 80 mg; and for pravastatin sodium, 10 mg, 20 mg, and 40 mg. The daily dosage amount for atorvastatin calcium may be in the range of, in one embodiment, from 1 mg to 160 mg and, in another embodiment, from 5 mg to 80 mg. Oral administration may be in a
10 single or divided doses of two, three, or four times daily, although a single daily dose of the HMG-CoA reductase inhibitor is preferred.

The compounds claimed herein can be utilized in methods for decreasing hyperglycemia and insulin resistance or for methods of treating type II diabetes. The compounds can be identified, formulated,
15 and administered as described above.

The methods claimed herein can be used effectively in combination with one or more additional active diabetes agents depending on the desired target therapy (see, e.g., Turner, N. et al. *Prog. Drug Res.* (1998) 51: 33-94; Haffner, S. *Diabetes Care* (1998) 21: 160-178; and
20 DeFronzo, R. et al. (eds.), *Diabetes Reviews* (1997) Vol. 5 No. 4). A number of studies have investigated the benefits of combination therapies with oral agents (see, e.g., Mahler, R., *J. Clin. Endocrinol. Metab.* (1999) 84: 1165-71; United Kingdom Prospective Diabetes Study Group: UKPDS 28, *Diabetes Care* (1998) 21: 87-92; Bardin, C. W., (ed.),
25 *CURRENT THERAPY IN ENDOCRINOLOGY AND METABOLISM*, 6th Edition (Mosby--Year Book, Inc., St. Louis, Mo. 1997); Chiasson, J. et al., *Ann. Intern. Med.* (1994) 121: 928-935; Coniff, R. et al., *Clin. Ther.* (1997) 19: 16-26; Coniff, R. et al., *Am. J. Med.* (1995) 98: 443-451; and Iwamoto, Y. et al, *Diabet. Med.* (1996) 13 365-370; Kwiterovich, P.

-140-

Am. J. Cardiol (1998) 82(12A): 3U-17U). These studies indicate that diabetes and hyperlipidemia modulation can be further improved by the addition of a second agent to the therapeutic regimen.

An example of combination therapy that modulates (prevents the onset of the symptoms or complications associated) atherosclerosis, is administered with one or more of the following active agents: an antihyperlipidemic agent; a plasma HDL-raising agent; an antihypercholesterolemic agent, such as a cholesterol biosynthesis inhibitor, e.g., an hydroxymethylglutaryl (HMG) CoA reductase inhibitor (also referred to as statins, such as lovastatin, simvastatin, pravastatin, fluvastatin, and atorvastatin), an HMG-CoA synthase inhibitor, a squalene epoxidase inhibitor, or a squalene synthetase inhibitor (also known as squalene synthase inhibitor); an acyl-coenzyme A cholesterol acyltransferase (ACAT) inhibitor, such as melinamide; probucol; nicotinic acid and the salts thereof and niacinamide; a cholesterol absorption inhibitor, such as β -sitosterol; a bile acid sequestrant anion exchange resin, such as cholestyramine, colestipol or dialkylaminoalkyl derivatives of a cross-linked dextran; an LDL (low density lipoprotein) receptor inducer; fibrates, such as clofibrate, bezafibrate, fenofibrate, and gemfibrizol; vitamin B₆ (also known as pyridoxine) and the pharmaceutically acceptable salts thereof, such as the HCl salt; vitamin B₁₂ (also known as cyanocobalamin); vitamin B₃ (also known as nicotinic acid and niacinamide, supra); anti-oxidant vitamins, such as vitamin C and E and beta carotene; a beta-blocker; an angiotensin II antagonist; an angiotensin converting enzyme inhibitor; and a platelet aggregation inhibitor, such as fibrinogen receptor antagonists (i.e., glycoprotein IIb/IIIa fibrinogen receptor antagonists) and aspirin.

Still another example of combination therapy can be seen in modulating diabetes (or treating diabetes and its related symptoms,

-141-

complications, and disorders) with, for example, sulfonylureas (such as chlorpropamide, tolbutamide, acetohexamide, tolazamide, glyburide, gliclazide, glynase, glimepiride, and glipizide), biguanides (such as metformin), thiazolidinediones (such as ciglitazone, pioglitazone, troglitazone, and rosiglitazone); and related insulin sensitizers, such as selective and non-selective activators of PPAR α , PPAR β and PPAR γ ; dehydroepiandrosterone (also referred to as DHEA or its conjugated sulphate ester, DHEA-SO₄); antiglucocorticoids; TNF α inhibitors; α -glucosidase inhibitors (such as acarbose, miglitol, and voglibose), pramlintide (a synthetic analog of the human hormone amylin), other insulin secretagogues (such as repaglinide, gliquidone, and nateglinide), insulin, as well as the active agents discussed above for treating atherosclerosis.

Further provided herein are methods for treating obesity, as well as treating the complications of obesity, by administering a compound claimed herein. The antagonists can be identified, formulated, and administered similarly to the information described above. A LXR selective antagonist includes a partial agonist/antagonist or antagonist that exhibits about a two to about a ten-fold preference for LXR α or β compared to another nuclear receptor such as, for example FXR with respect to potency (IC₅₀, the concentration of compound that achieves 50% of the maximum reduction in the transcription activity achieved by the compound of interest observed in the presence of a sub-maximal concentration of LXR agonist) and/or efficacy (the maximum percent inhibition of transcription observed with the compound in question).

Another example of combination therapy can be seen in treating obesity or obesity-related disorders, wherein the methods can be effectively used in combination with, for example, phenylpropanolamine, phentermine, diethylpropion, mazindol; fenfluramine, dexfenfluramine,

-142-

phentiramine, β_3 adrenoceptor agonist agents; sibutramine, gastrointestinal lipase inhibitors (such as orlistat), and leptins. Other agents used in treating obesity or obesity-related disorders include neuropeptide Y, enterostatin, cholecystokinin, bombesin, amylin, 5 histamine H_3 receptors, dopamine D_2 receptors, melanocyte stimulating hormone, corticotrophin releasing factor, galanin and gamma amino butyric acid (GABA).

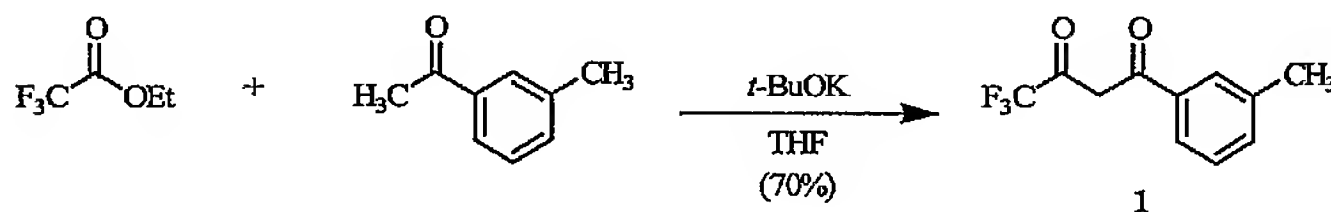
-143-

The following examples are offered by way of illustration and not by way of limitation.

Starting materials in the synthesis examples below are either available from commercial sources or via literature procedures. All commercially available compounds were used without further purification unless otherwise indicated. CDCl₃ (99.8% D, Cambridge Isotope Laboratories) was used in all experiments as indicated. ¹H NMR spectra were recorded on a Bruker Avance 400 MHz NMR spectrometer. Significant peaks are tabulated and typically include: number of protons, multiplicity (s, singlet; d, double; t, triplet; q, quartet; m, multiplet; br s, broad singlet) and coupling constant(s) in Hertz. Chemical shifts are reported as parts per million (δ) relative to tetramethylsilane. Electron Ionization (EI) mass spectra were recorded on a Perkin-Elmer SCIEX HPLC/MS instrument using reverse-phase conditions (acetonitrile/water, 0.05% trifluoroacetic acid). Abbreviations used in the examples below have their accepted meanings in the chemical literature. For example, CH₂Cl₂ (dichloromethane), C₆H₆ (benzene), TFA (trifluoroacetic acid), EtOAc (Ethyl Acetate), Et₂O (diethyl ether), DMAP (4-dimethylaminopyridine), DMF (N,N-dimethylformamide) and THF (tetrahydrofuran). Flash chromatography was performed using Merck Silica Gel 60 (230-400 mesh) according to Still *et. al.*¹

EXAMPLE 1

This example illustrates the preparation of compound 1.



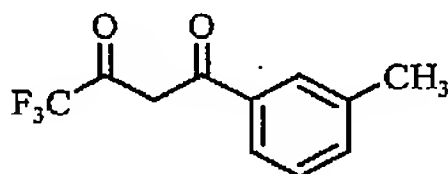
Potassium *tert*-butoxide (3.3 g, 28 mmoles, 95% powder) was slowly added to a solution of 3-methylacetophenone (3.2 mL, 23.5 mmoles) in anhydrous THF at 0 °C under nitrogen. The vigorously stirred mixture was

-144-

allowed to warm to ambient temperature and was stirred at this temperature for 15 min. After this period the mix was chilled to 0 °C and to it was added ethyl trifluoroacetate (3.4 mL, 28.6 mmoles). The stirring mixture was next allowed the warm to ambient temp and was stirred for 12 hours. After this

5 period the reaction was evaporated *in vacuo* (-THF) and the resulting residue was combined with 30 mL of water. 10% sulfuric acid was carefully added to the stirring mixture to adjust the to pH 6-7 (as indicated using EM Science colorpHast indicator strips, pH 0-14). The mixture was then extracted with Et₂O (3 x 15mL). The combined ether layer was next washed with water (2 x

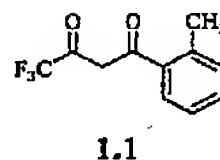
10 15 mL) and brine (15 mL). After drying the ether layer over anhydrous Na₂SO₄ the solution was evaporated *in vacuo* to yield the crude product as a yellow liquid. The product was purified via vacuum fractional distillation to yield 3.7 g (70% yield) of product as a clear liquid. B.P. 64 °C @ 0.05 mmHg



1
4,4,4-Trifluoro-1-*m*-tolyl-butane-1,3-dione

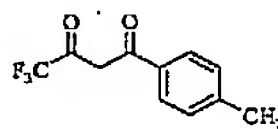
15 ¹H-NMR (CDCl₃): δ 15.16 (bs, 1H), 7.76 (s, 1H), 7.74 (d, J=7.2Hz, 1H), 7.45-7.38 (m, 2H), 6.56 (s, 1H), 2.44 (s, 3H).

The following compounds were prepared in a manner similar to that described above.



1.1

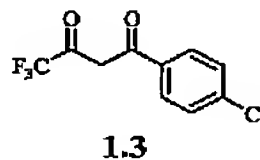
20 ¹H-NMR (CDCl₃): δ 15.0 (br, 1H), 7.60 (m, 1 H), 7.47 (m, 1 H), 7.33 (m, 2 H), 6.36 (s, 1 H), 2.57 (s, 3 H).



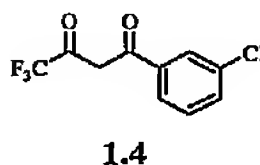
1.2

-145-

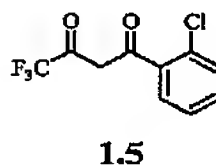
$^1\text{H-NMR}$ (CDCl_3): δ 15.1 (br, 1 H), 7.83 (d, $J = 8.2$ Hz, 2 H), 7.29 (d, $J = 8.2$ Hz, 2 H), 6.52 (s, 1 H), 2.43 (s, 3 H).



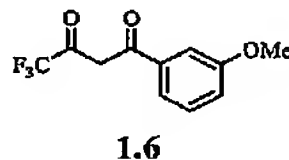
$^1\text{H-NMR}$ (CDCl_3): δ 14.8 (br, 1 H), 7.71 (d, $J = 8.6$ Hz, 2 H), 7.33 (d, $J = 8.6$ Hz, 2 H), 6.30 (s, 1 H).



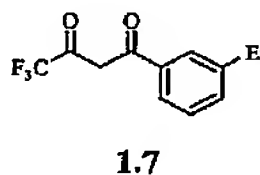
$^1\text{H-NMR}$ (CDCl_3): δ 14.7 (br, 1 H), 7.90 (m, 1 H), 7.80 (d, $J = 8.0$ Hz, 1 H), 7.57 (d, $J = 8.0$ Hz, 1 H), 7.44 (m, 1 H), 6.52 (s, 1 H).



$^1\text{H-NMR}$ (CDCl_3): δ 14.4 (br, 1 H), 7.68 (m, 1H), 7.48 (m, 1 H), 7.47 (m, 1 H), 7.39 (m, 1 H), 6.56 (s, 1 H).

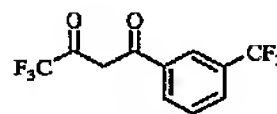


$^1\text{H-NMR}$ (CDCl_3): δ 15.09 (br, 1 H), 7.51 (m, 1 H), 7.46 (m, 1 H), 7.41 (m, 1 H), 7.16 (m, 1 H), 6.56 (s, 1 H), 3.88 (s, 3 H).



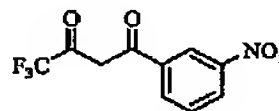
-146-

$^1\text{H-NMR}$ (CDCl_3): δ 15.18 (br, 1 H), 7.77 (m, 1 H), 7.75 (m, 1 H), 7.46 (m, 1 H), 7.43 (m, 1 H), 6.57 (s, 1 H), 2.73 (q, $J = 7.7$ Hz, 2 H), 1.28 (t, $J = 7.7$ Hz, 3 H).



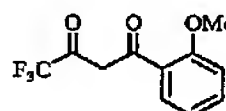
1.8

5 $^1\text{H-NMR}$ (CDCl_3): δ 14.89 (br, 1 H), 8.19 (s, 1 H), 8.13 (d, $J = 8.1$, 1 H), 7.88 (d, $J = 8.3$ Hz, 1 H), 7.67 (m, 1 H), 6.60 (s, 1 H).



1.9

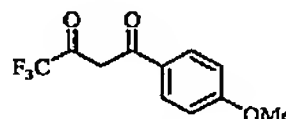
10 $^1\text{H-NMR}$ (CDCl_3): δ 14.75 (br, 1H), 8.78 (m, 1H), 8.48 (m, 1H), 8.29 (m, 1 H), 7.76 (t, $J = 8$ Hz, 1 H), 6.66 (s, 1H).



1.10

$^1\text{H-NMR}$ (CDCl_3): δ 15.25 (br, 1H), 8.0 (m, 1 H), 7.56 (m, 1 H), 7.10 (m, 1 H), 7.02 (m, 1 H), 3.98 (s, 3 H).

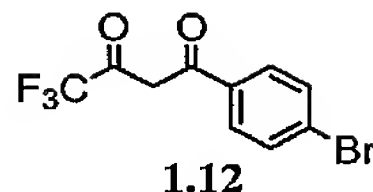
15



1.11

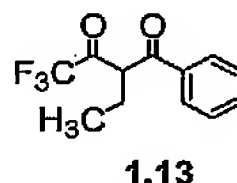
$^1\text{H-NMR}$ (CDCl_3): δ 15.4 (br, 1H), 7.92 (d, $J = 8.8$ Hz, 2 H), 6.97 (d, $J = 8.8$ Hz, 2 H), 6.48 (s, 1 H), 3.89 (s, 3 H).

-147-



1-(4-Bromo-phenyl)-4,4,4-trifluoro-
butane-1,3-dione

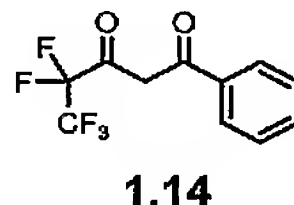
$^1\text{H-NMR}$ (CDCl_3): δ 15.0 (s, 1H), 7.82 (d, $J=8.6\text{Hz}$, 2H), 7.66 (d, $J=8.6\text{Hz}$, 2H), 6.54 (s, 1H).



2-Ethyl-4,4,4-trifluoro-1-phenyl-
butane-1,3-dione

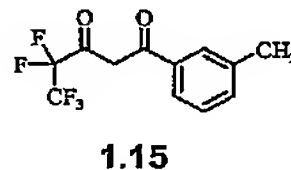
5

$^1\text{H-NMR}$ (CDCl_3): δ 8.05 (bd, $J'=8.1\text{Hz}$, 2H), 7.55 (tt, $J'=7.6\text{Hz}$, $J''=1.3\text{Hz}$, 1H), 7.45 (bt, $J=7.3\text{Hz}$, 2H), 4.38 (q, $J=7.1\text{Hz}$, 2H), 1.4 (t, $J=7.1\text{Hz}$, 3H).



4,4,5,5,5-Pentafluoro-1-phenyl-
pentane-1,3-dione

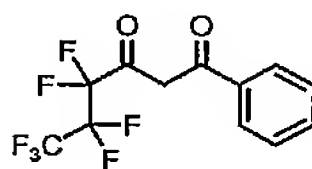
10 $^1\text{H-NMR}$ (CDCl_3): δ 15.32 (bs, 1H), 7.99-7.94 (m, 2H), 7.64 (m, 1H), 7.55-7.48 (m, 2H), 6.64 (s, 1H).



4,4,5,5,5-Pentafluoro-1-*m*-tolyl-
pentane-1,3-dione

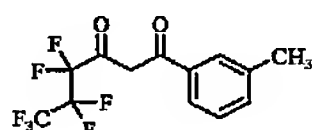
-148-

$^1\text{H-NMR}$ (CDCl_3): δ 15.35 (bs, 1H), 7.79-7.73 (m, 2H), 7.47-7.36 (m, 2H), 6.63 (s, 1H), 2.44 (s, 3H).

**1.16**

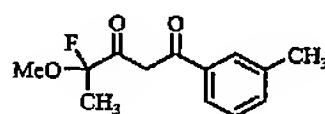
4,4,5,5,6,6,6-Heptafluoro-1-phenyl-hexane-1,3-dione

$^1\text{H-NMR}$ (CDCl_3): δ 15.33 (bs, 1H), 7.99-7.94 (m, 2H), 7.67-7.61 (m, 1H), 7.55-7.50 (m, 2H), 6.62 (s, 1H),

5**1.17**

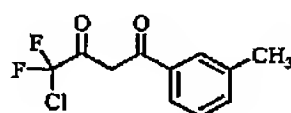
4,4,5,5,6,6,6-Heptafluoro-1-*m*-tolyl-hexane-1,3-dione

$^1\text{H-NMR}$ (CDCl_3): δ 15.33 (bs, 1H), 7.79-7.73 (m, 2H), 7.47-7.36 (m, 2H), 6.61 (s, 1H), 2.45 (s, 3H).

**1.18**

4-Fluoro-4-methoxy-1-*m*-tolyl-pentane-1,3-dione

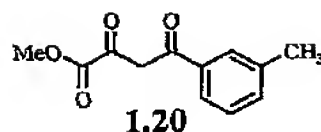
$^1\text{H-NMR}$ (CDCl_3): δ 15.65 (s, 1H), 7.79-7.74 (m, 2H), 7.45-7.36 (m, 2H), 6.68 (d, $J=2.0\text{Hz}$, 1H), 3.61 (s, 3H), 2.44 (s, 3H).

10**1.19**

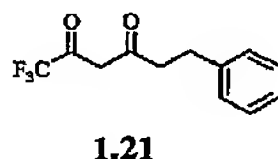
4-Chloro-4,4-difluoro-1-*m*-tolyl-butane-1,3-dione

$^1\text{H-NMR}$ (CDCl_3): δ 14.95 (s, 1H), 7.76-7.71 (m, 2H), 7.45-7.36 (m, 2H), 6.52 (s, 1H), 2.44 (s, 3H).

-149-

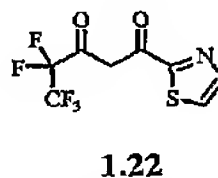
2,4-Dioxo-4-*m*-tolyl-butylric acid methyl ester

$^1\text{H-NMR}$ (CDCl_3): δ 15.3 (s, 1H), 7.83-7.78 (m, 2H), 7.45-7.36 (m, 2H), 7.08 (s, 1H), 3.95 (s, 3H), 2.44 (s, 3H).



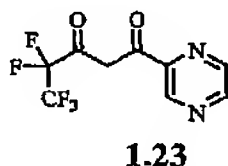
1,1,1-Trifluoro-6-phenyl-hexane-2,4-dione

5 $^1\text{H-NMR}$ (CDCl_3): δ 14.3 (s, 1H), 7.34-7.15 (m, 5H), 5.89 (s, 1H), 2.98 (t, 8.1Hz, 2H), 2.76 (t, $J=7.6\text{Hz}$, 2H).



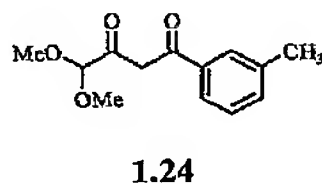
4,4,5,5,5-Pentafluoro-1-thiazol-2-yl-pentane-1,3-dione

$^1\text{H-NMR}$ (CDCl_3): δ 14.3 (bs, 1H), 8.09 (d, $J=3.0\text{Hz}$, 1H), 7.80 (d, $J=3.0\text{Hz}$, 1H), 7.04 (bs, 1H).



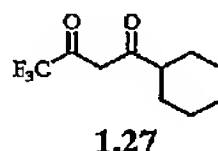
10 4,4,5,5,5-Pentafluoro-1-pyrazin-2-yl-pentane-1,3-dione

$^1\text{H-NMR}$ (CDCl_3): δ 14.5 (bs, 1H), 9.34 (d, $J=1.3\text{Hz}$, 1H), 8.81 (d, $J=2.3\text{Hz}$, 1H), 8.71 (dd, $J'=2.3\text{Hz}$, $J''=1.3\text{Hz}$, 1H), 7.32 (s, 1H).

4,4-Dimethoxy-1-*m*-tolyl-butane-1,3-dione

-150-

$^1\text{H-NMR}$ (CDCl_3): δ 15.8 (s, 1H), 7.75 (s, 2H), 7.36 (m, 3H), 6.56 (s, 1H), 4.83 (s, 1H), 3.45 (s, 3H).

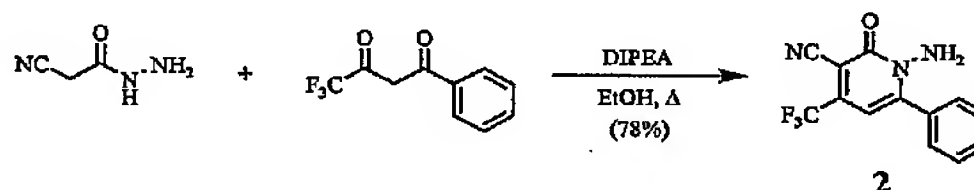


1-Cyclohexyl-4,4,4-trifluoro-butane-1,3-dione

5 $^1\text{H-NMR}$ (CDCl_3): δ 5.92 (s, 1H), 2.33 (tt, $J'=3.3\text{Hz}$, $J''=11.4\text{Hz}$, 1H), 1.94-1.63 (m, 5H), 1.47-1.16 (m, 5H).

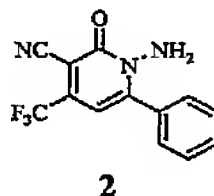
EXAMPLE 2

This example illustrates the preparation of compound 2.



10 4,4,4-Trifluoro-1-phenyl-1,3-butanedione (2.0 g, 9.25 mmoles) and cyanoacetohydrazide (0.92 g, 9.28 mmoles) were combined within a round-bottom flask.

The mixture was dissolved into 30 mL of ethanol and the flask was equipped with a reflux condensor. To the stirring solution was added
 15 diisopropylethylamine (0.81 mL, 4.7 mmoles) and the mixture was stirred at 80 °C for 3 hours. After this period the mixture was evaporated and the resulting crude mixture was purified directly by flash silica chromatography using 30% EtOAc/Hexane to yield product 2.01 g (78% yield) as a yellow solid.

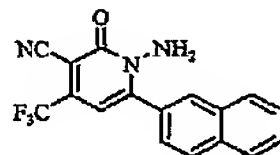


1-Amino-2-oxo-6-phenyl-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile

-151-

$^1\text{H-NMR}$ (CDCl_3): δ 7.63-7.54 (m, 5H), 6.53 (s, 1H), 5.68 (s, 2H).
 MS (ES⁺): 280.0 (M+H).

The following compounds were prepared in a manner similar to that described above.

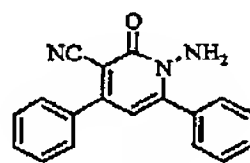


2.1

5

1-Amino-6-naphthalen-2-yl-2-oxo-4-trifluoromethyl-
 1,2-dihydro-pyridine-3-carbonitrile

$^1\text{H-NMR}$ (CDCl_3): δ 8.03 (s, 1H), 7.93 (d, J=8.6Hz, 1H), 7.89-7.85 (m, 2H), 7.62-7.52 (m, 3H), 6.56 (s, 1H), 5.67 (s, 2H).

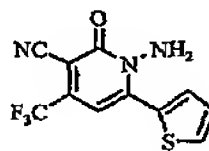


2.2

1-Amino-2-oxo-4,6-diphenyl-1,2-dihydro-pyridine-3-carbonitrile

10

$^1\text{H-NMR}$ (CDCl_3): δ 7.65 – 7.58 (m, 4 H), 7.56 – 7.46 (m, 6 H), 6.38 (s, 1H), 5.40 (s, 2 H). MS (ES⁺):288.0 (M+H)



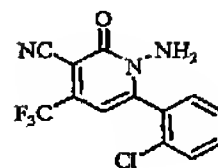
2.3

15

1-Amino-2-oxo-6-thiophen-2-yl-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile

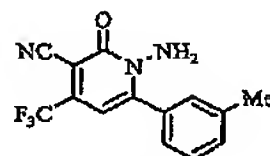
$^1\text{H-NMR}$ (CDCl_3): δ 7.95 (m, 1 H), 7.79 (m, 1 H), 7.26 (m, 1 H), 6.91 (s, 1 H), 5.47 (s, 2H). MS (ES⁺):286.0 (M+H)

-152-



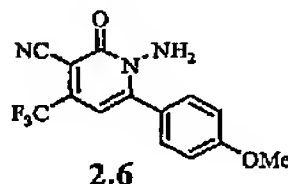
2.4

$^1\text{H-NMR}$ (CDCl_3): δ 7.57 (m, 1H), 7.56 (m, 1H), 7.49 (m, 1H), 7.39 (m, 1 H), 6.50 (s, 1H), 5.54 (s, 2H).



2.5

5 $^1\text{H-NMR}$ (CDCl_3): δ 7.46 – 7.37 (m, 4H), 6.52 (s, 1H), 5.81 (s, 2H), 2.45 (s, 3H).



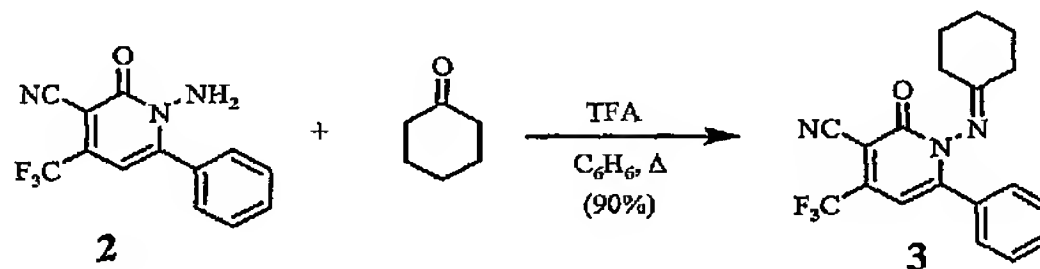
2.6

$^1\text{H-NMR}$ (CDCl_3): δ 7.64 (d, J = 9.0 Hz, 2H), 7.05 (d, J = 9.0 Hz, 2H), 6.51 (s, 1H), 5.78 (s, 2H), 3.90 (s, 3H).

10

EXAMPLE 3

This example illustrates the preparation of compound 3.



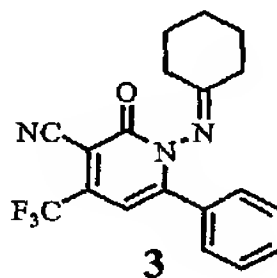
15 N-Aminopyridone 2 (70 mg, 0.25 mmoles) was dissolved into 3.0 mL of benzene* within a screw capped vial. To this solution was added cyclohexanone 0.4 mL, 3.9 mmoles) and 2 mL of trifluoroacetic acid. The sealed reaction was then shaken at 85 °C for 2 hours. After this period the reaction mixture was evaporated *in vacuo* and the resulting residue was

-153-

combined with DCM. The DCM solution was washed with sat'd NaHCO₃ (2 x 10 mL), dried over anhydrous Na₂SO₄, and was evaporated to yield the crude product. The crude product was purified using flash silica chromatography (30% EtOAc/Hexane) to yield 82 mg (90% yield) of product as a yellow

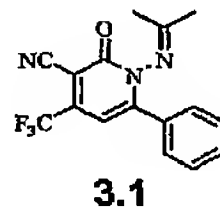
5 residue.

(* - DCM may be used as an alternative with heating at 50 °C)

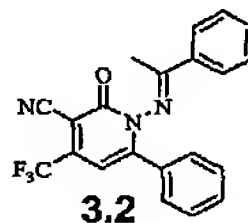


¹H-NMR (CDCl₃): δ 7.53-7.45 (m, 3H), 7.41-7.39 (m, 2H), 6.50 (s, 1H), 2.47-2.44 (m, 1H), 2.39-2.34 (m, 1H), 2.20-2.14 (m, 1H), 2.07-2.02 (m, 1H), 1.88-1.85 (m, 2H), 1.60-1.55 (m, 2H), 1.44-1.42 (m, 1H), 1.35-1.31 (m, 1H). MS (ES⁺): 360.0 (M+H)

The following compounds were prepared in a manner similar to that described above.

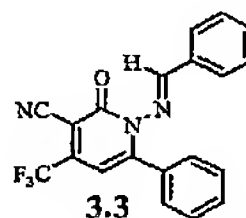


¹H-NMR (CDCl₃): δ 7.52-7.47 (m, 3H), 7.40-7.37 (m, 2H), 6.50 (s, 1H), 2.12 (s, 3H), 1.85 (s, 3H). MS (ES⁺): 320.0 (M+H).



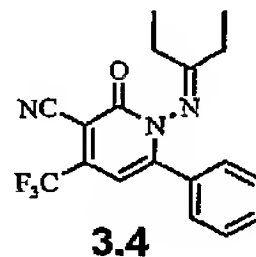
-154-

$^1\text{H-NMR}$ (CDCl_3): δ 7.68 (dd, $J'=8.4\text{Hz}$, $J''=1.2\text{Hz}$, 2H), 7.49-7.43 (m, 6H), 7.38 (t, $J=8\text{Hz}$, 2H), 6.58 (s, 1H), 2.27 (s, 3H). MS (ES⁺): 382.0 (M+H).



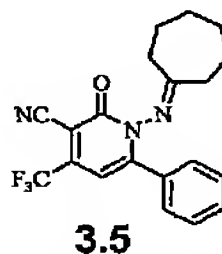
1-(Benzylidene-amino)-2-oxo-6-phenyl-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile

5 $^1\text{H-NMR}$ (CDCl_3): δ 8.97 (s, 1H), 7.66 (dd, $J'=7.6\text{Hz}$, $J''=0.8\text{Hz}$, 2H), 7.54-7.41 (m, 8H), 6.57 (s, 1H). MS (ES⁺): 368.0 (M+H).



1-(1-Ethyl-propylideneamino)-2-oxo-6-phenyl-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile

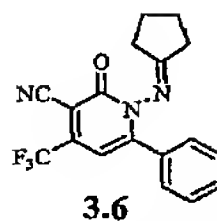
10 $^1\text{H-NMR}$ (CDCl_3): δ 7.52-7.41 (m, 5H), 6.49 (s, 1H), 2.52-2.44 (m, 1H), 2.38-2.31 (m, 1H), 2.18-2.10 (m, 1H), 2.01-1.92 (m, 1H), 1.02-0.97 (m, 6H). MS (ES⁺): 348.0 (M+H).



1-Cycloheptylideneamino-2-oxo-6-phenyl-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile

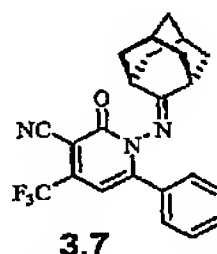
$^1\text{H-NMR}$ (CDCl_3): δ 7.54-7.44 (m, 5H), 6.49 (s, 1H), 2.62-2.54 (m, 2H), 2.45-2.39 (m, 1H), 2.08-2.00 (m, 1H), 1.75-1.45 (m, 6H), 1.12-1.06 (m, 2H). MS (ES⁺): 374.0 (M+H).

-155-



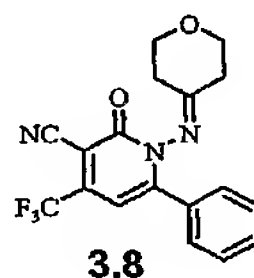
1-Cyclopentylideneamino-2-oxo-6-phenyl-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile

$^1\text{H-NMR}$ (CDCl_3): δ 7.54-7.45 (m, 3H), 7.40 (dd, $J'=8\text{Hz}$, $J''=1.2\text{Hz}$, 2H), 2.85-2.0 (m, 8H). MS (ES $^+$): 346.0 (M+H).

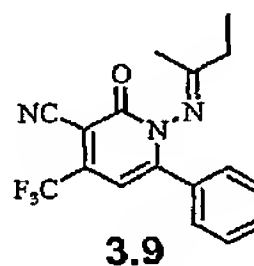


1-(Adamantan-2-ylideneamino)-2-oxo-6-phenyl-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile

5 $^1\text{H-NMR}$ (CDCl_3): δ 7.53-7.45 (m, 5H), 6.49 (s, 1H), 2.82 (bs, 1H), 2.37 (bs, 1H), 2.21 (d, $J=12.5\text{Hz}$, 1H), 2.14 (d, $J=12.8\text{Hz}$, 1H), 2.03-1.99 (m, 2H), 1.90-1.76 (m, 6H), 1.25 (d, $J=12.8\text{Hz}$, 1H), 1.08 (d, $J=12.5\text{Hz}$, 1H). MS (ES $^+$): 412.2 (M+H).

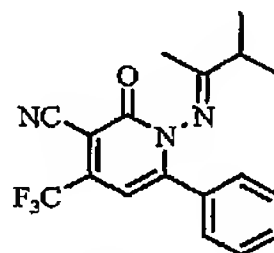


10 $^1\text{H-NMR}$ (CDCl_3): δ 7.56-7.47 (m, 3H), 7.40-7.37 (m, 2H), 6.52 (s, 1H), 3.95-3.89 (m, 2H), 3.69-3.65 (m, 1H), 3.58-3.54 (m, 1H), 2.68-2.63 (m, 1H), 2.47-2.35 (m, 2H), 2.16-2.12 (m, 1H). MS (ES $^+$): 261.8 (M+H).

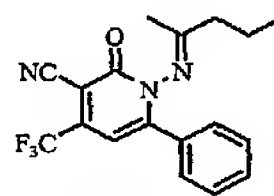


-156-

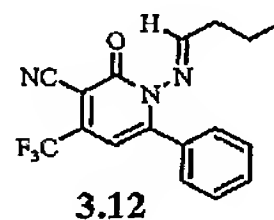
$^1\text{H-NMR}$ (CDCl_3): δ 7.51-7.44 (m, 3H), 7.42-7.38 (2H), 6.50 (s, 1H), 2.55-2.45 (m, 1H), 2.40-2.25 (m, 1H), 1.81 (s, 3H), 1.01 (t, $J=7.6\text{Hz}$, 3H). MS (ES $^+$): 334.2 (M+H).

**3.10**

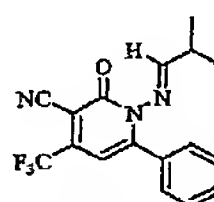
5 $^1\text{H-NMR}$ (CDCl_3): δ 7.51-7.43 (m, 3H), 7.39-7.37 (m, 2H), 6.50 (s, 1H), 2.63 (m, $J=6.9\text{Hz}$, 1H), 1.78 (s, 3H), 1.04 (d, $J=6.9\text{Hz}$, 3H), 1.00 (d, $J=6.9\text{Hz}$, 3H).

**3.11**

10 $^1\text{H-NMR}$ (CDCl_3): δ 7.52-7.44 (m, 3H), 7.40-7.37 (m, 2H), 6.50 (s, 1H), 2.40-2.30 (m, 2H), 1.81 (s, 3H), 1.53-1.45 (m, 2H), 0.80 (t, $J=7.4\text{Hz}$, 3H).

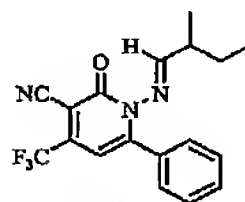
**3.12**

15 $^1\text{H-NMR}$ (CDCl_3): δ 8.16 (t, $J=5.4\text{Hz}$, 1H), 7.53-7.45 (m, 3H), 7.42-7.38 (m, 2H), 6.48 (s, 1H), 2.47-2.42 (m, 2H), 1.61-1.52 (m, 2H), 0.89 (t, $J=7.4\text{Hz}$, 3H). MS (ES $^+$): 334.2 (M+H).

**3.13**

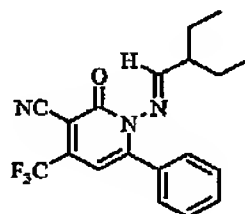
-157-

$^1\text{H-NMR}$ (CDCl_3): δ 8.07 (d, $J=5.2\text{Hz}$, 1H), 7.51-7.45 (m, 3H), 7.41-7.38 (m, 2H), 6.49 (s, 1H), 2.78-2.65 (m, 1H), 1.09 (d, $J=6.8\text{Hz}$, 6H).

**3.14**

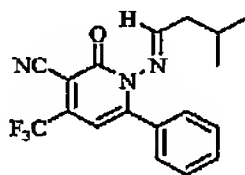
1-(2-Methyl-butylideneamino)-2-oxo-6-phenyl-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile

5 $^1\text{H-NMR}$ (CDCl_3): δ 8.01 (d, $J=6.2\text{Hz}$, 1H), 7.53-7.44 (m, 3H), 7.42-7.39 (m, 2H), 6.48 (s, 1H), 2.53-2.44 (m, $J=6.8\text{Hz}$, 1H), 1.53-1.40 (m, 2H), 1.06 (d, $J=6.8\text{Hz}$, 3H), 0.86 (t, $J=7.5\text{Hz}$, 3H).

**3.15**

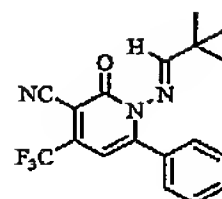
1-(2-Ethyl-butylideneamino)-2-oxo-6-phenyl-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile

10 $^1\text{H-NMR}$ (CDCl_3): δ 7.92 (d, $J=7.4\text{Hz}$, 1H), 7.52-7.40 (m, 5H), 6.47 (s, 1H), 2.29-2.23 (m, 1H), 1.57-1.44 (m, 4H), 0.81 (t, $J=7.4$, 6H).
MS (ES⁺): 362.0 (M+H).

**3.16**

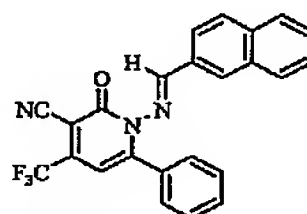
1-(3-Methyl-butylideneamino)-2-oxo-6-phenyl-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile

15 $^1\text{H-NMR}$ (CDCl_3): δ 8.15 (t, $J=5.9\text{Hz}$, 1H), 7.53-7.44 (m, 3H), 7.42-7.39 (m, 2H), 6.48 (s, 1H), 2.34 (t, $J=5.9\text{Hz}$, 2H), 1.96 (m, $J=6.7\text{Hz}$, 1H), 0.91 (d, $J=6.7\text{Hz}$, 6H).

-158-**3.17**

1-(2,2-Dimethyl-propylideneamino)-2-oxo-6-phenyl-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile

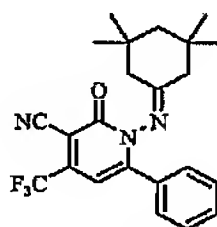
$^1\text{H-NMR}$ (CDCl_3): δ 8.03 (s, 1H), 7.51-7.44 (m, 3H), 7.40-7.38 (m, 2H), 6.49 (s, 1H), 1.08 (s, 9H). MS (ES⁺): 348.0 (M+H).

**3.18**

1-[(Naphthalen-2-ylmethylene)-amino]-2-oxo-6-phenyl-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile

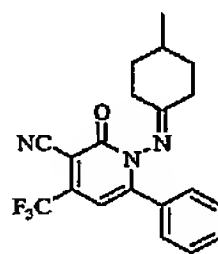
5

$^1\text{H-NMR}$ (CDCl_3): δ 9.12 (s, 1H), 8.09 (s, 1H), 7.91-7.74 (m, 4H), 7.62-7.44 (m, 7H), 6.59 (s, 1H). MS (ES⁺): 418.0 (M+H).

**3.19**

2-Oxo-6-phenyl-1-(3,3,5,5-tetramethyl-cyclohexylideneamino)-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile

MS(ES⁺): 416.0 (M+H)

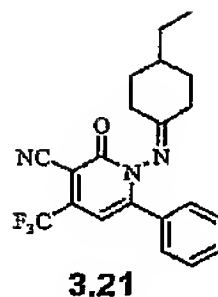
**3.20**

1-(4-Methyl-cyclohexylideneamino)-2-oxo-6-phenyl-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile

10

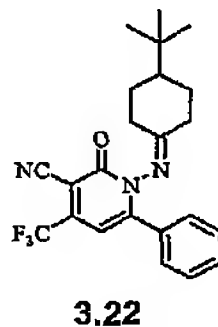
MS(ES⁺): 374.0 (M+H)

-159-



1-(4-Ethyl-cyclohexylideneamino)-2-oxo-6-phenyl-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile

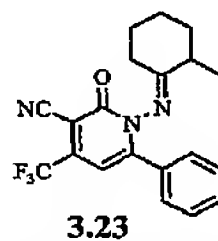
MS(ES⁺): 388.0 (M+H)



1-(4-*tert*-Butyl-cyclohexylideneamino)-2-oxo-6-phenyl-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile

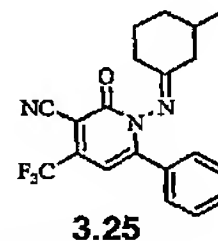
5

MS(ES⁺): 416.2 (M+H)



1-(2-Methyl-cyclohexylideneamino)-2-oxo-6-phenyl-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile

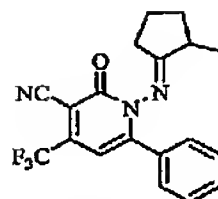
MS(ES⁺): 374.0 (M+H)



1-(3-Methyl-cyclohexylideneamino)-2-oxo-6-phenyl-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile

MS(ES⁺): 374.0 (M+H)

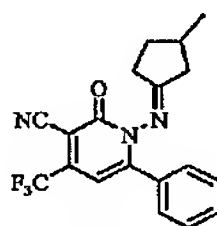
-160-



3.26

1-(2-Methyl-cyclopentylideneamino)-2-oxo-6-phenyl-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile

MS(ES⁺): 360.0 (M+H)

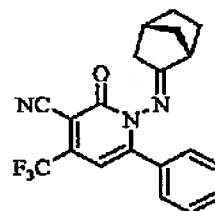


3.27

1-(3-Methyl-cyclopentylideneamino)-2-oxo-6-phenyl-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile

5

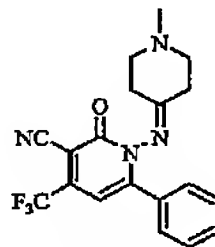
MS(ES⁺): 360.0 (M+H)



3.28

1-(Bicyclo[2.2.1]hept-2-ylideneamino)-2-oxo-6-phenyl-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile

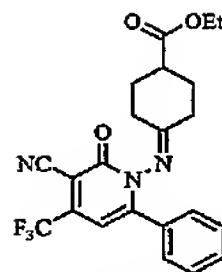
MS(ES⁺): 372.0 (M+H)



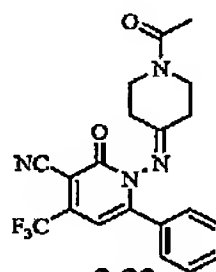
3.29

1-(1-Methyl-piperidin-4-ylideneamino)-2-oxo-6-phenyl-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile

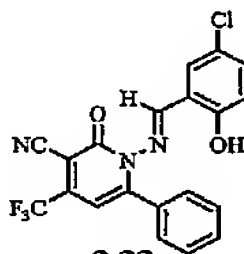
MS(ES⁺): 375.0 (M+H)

-161-**3.30**

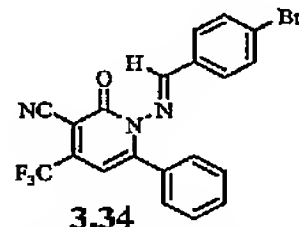
4-(3-Cyano-2-oxo-6-phenyl-4-trifluoromethyl-2*H*-pyridin-1-ylimino)-
cyclohexanecarboxylic acid ethyl ester

MS(ES⁺): 432.2 (M+H)**3.32**

1-(1-Acetyl-piperidin-4-ylideneamino)-2-oxo-6-phenyl-4-
trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile

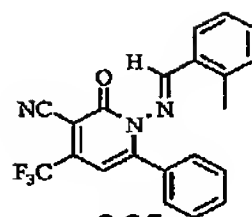
MS(ES⁺): 403.0 (M+H)**3.33**

1-[(5-Chloro-2-hydroxy-benzylidene)-amino]-2-oxo-6-phenyl-4-
trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile

5MS(ES⁺): 418.0 (M+H)**3.34**

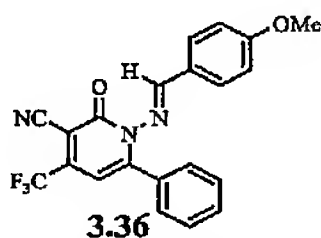
1-[(4-Bromo-benzylidene)-amino]-2-oxo-6-phenyl-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbon

MS(ES⁺): 446.0 (M+H)

-162-

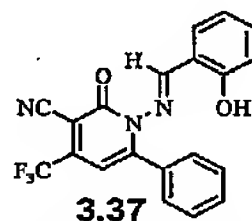
1-[(2-Methyl-benzylidene)-amino]-2-oxo-6-phenyl-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile

MS(ES⁺): 382.2 (M+H)



1-[(4-Methoxy-benzylidene)-amino]-2-oxo-6-phenyl-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile

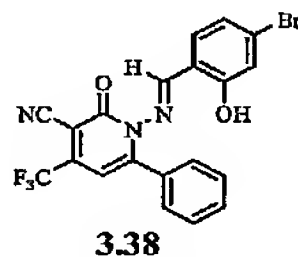
MS(ES⁺): 398.0 (M+H)



1-[(2-Hydroxy-benzylidene)-amino]-2-oxo-6-phenyl-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile

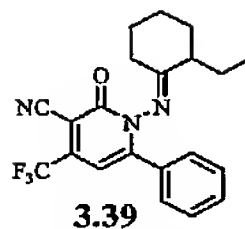
5

MS(ES⁺): 384.0 (M+H)



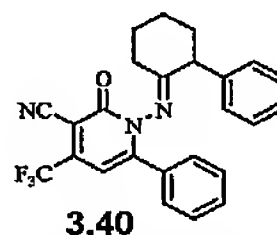
1-[(4-Bromo-2-hydroxy-benzylidene)-amino]-2-oxo-6-phenyl-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile

MS(ES⁺): 462.0 (M+H)

-163-

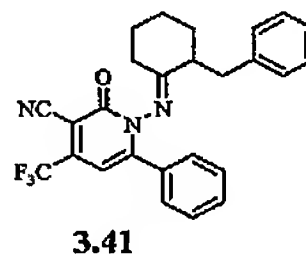
1-(2-Ethyl-cyclohexylideneamino)-2-oxo-6-phenyl-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile

MS(ES⁺): 388.0 (M+H)



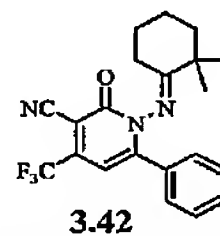
2-Oxo-6-phenyl-1-(2-phenyl-cyclohexylideneamino)-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile

MS(ES⁺): 436.2 (M+H)



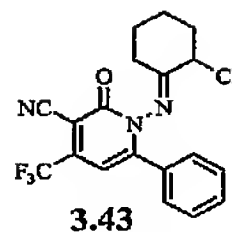
1-(2-Benzyl-cyclohexylideneamino)-2-oxo-6-phenyl-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile

MS(ES⁺): 450.2 (M+H)

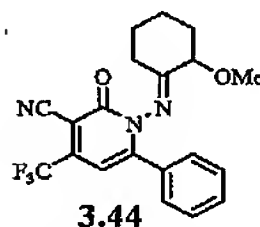


1-(2,2-Dimethyl-cyclohexylideneamino)-2-oxo-6-phenyl-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile

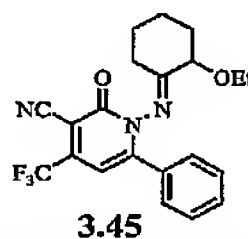
MS(ES⁺): 388.0 (M+H)

-164-

1-(2-Chloro-cyclohexylideneamino)-2-oxo-6-phenyl-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile

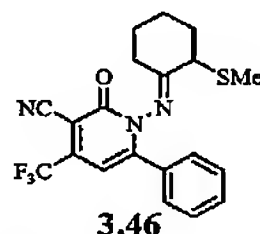
MS(ES⁺): 393.8 (M+H)

1-(2-Methoxy-cyclohexylideneamino)-2-oxo-6-phenyl-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile

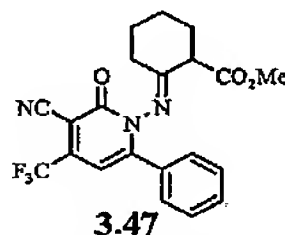
MS(ES⁺): 390.2 (M+H)

1-(2-Ethoxy-cyclohexylideneamino)-2-oxo-6-phenyl-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile

5

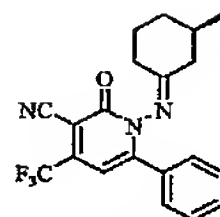
MS(ES⁺): 404.0 (M+H)

1-(2-Methylsulfanyl-cyclohexylideneamino)-2-oxo-6-phenyl-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile

MS(ES⁺): 406.2 (M+H)

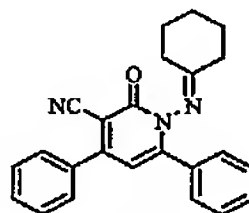
2-(3-Cyano-2-oxo-6-phenyl-4-trifluoromethyl-2H-pyridin-1-ylimino)-cyclohexanecarboxylic acid methyl ester

-165-

MS(ES⁺): 418.0 (M+H)

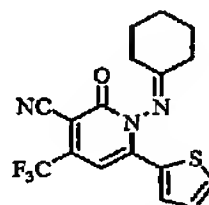
3.48

1-(3-Methyl-cyclohexylideneamino)-2-oxo-6-phenyl-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile

MS(ES⁺): 374.0 (M+H)

3.49

- 5 ¹H-NMR (CDCl₃): δ 7.60 (m, 2H), 7.44 (m, 4 H), 7.36 (m, 4H), 6.30 (s, 1H), 2.40 (m, 1H), 2.30 (m, 1H), 2.16 (m, 1H), 2.10 (m, 1H), 1.80 (m, 2H), 1.63 (m, 1H), 1.53 (m, 1H), 1.32 (m, 1H).

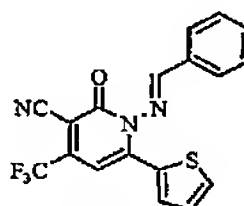


3.50

- 10 1-Cyclohexylideneamino-2-oxo-6-thiophen-2-yl-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile

MS (ES⁺):366.2 (M+H)

- ¹H-NMR (CDCl₃): δ 7.77 (m, 2H), 7.74 (m, 1H), 7.21 (m, 1H), 6.89 (s, 1H), 2.72 (m, 2H), 2.23 (m, 1H), 2.10 (m, 1H), 2.03 (m, 1H), 1.87 (m, 2H), 1.68 (m, 2H), 1.44 (m, 1H).

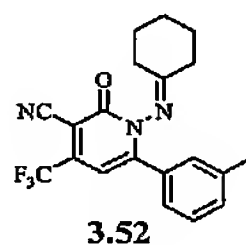


3.51

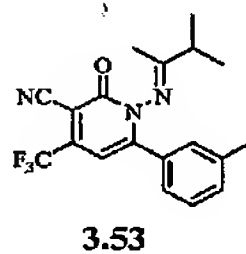
15

-166-

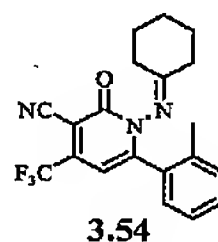
$^1\text{H-NMR}$ (CDCl_3): δ 8.89 (s, 1H), 7.88 (m, 1H), 7.86 (m, 1H), 7.74 (m, 1H), 7.66 (m, 1H), 7.56 (m, 1H), 7.46 (m, 2H), 7.12 (m, 1H), 6.89 (s, 1H).



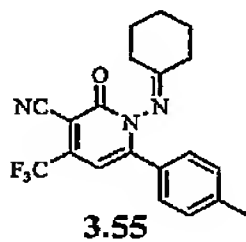
$^1\text{H-NMR}$ (CDCl_3): δ 7.35 (m, 1H), 7.32 (m, 1H), 7.20 (m, 1H), 7.19 (m, 1H), 6.49 (s, 1H), 2.48 (m, 1H), 2.41 (s, 3H), 2.38 (m, 1H), 2.20 (m, 1H), 2.07 (m, 1H), 1.88 (m, 2H), 1.61 (m, 2H), 1.46 (m, 1H), 1.37 (m, 1H).



$^1\text{H-NMR}$ (CDCl_3): δ 7.33 (m, 1H), 7.31 (m, 1H), 7.19 (m, 1H), 7.17 (m, 1H), 6.49 (s, 1H), 2.64 (m, $J = 6.8$ Hz, 1H), 2.40 (s, 3H), 1.79 (s, 3H), 1.06 (d, $J = 6.8$ Hz, 3H), 1.02 (d, $J = 6.8$ Hz, 3H).

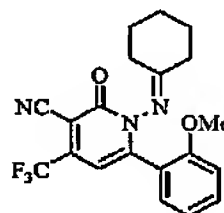


$^1\text{H-NMR}$ (CDCl_3): δ 7.39 (m, 1H), 7.29 (m, 1H), 7.23 (m, 1H), 6.96 (m, 1H), 6.43 (s, 1H), 2.37 (m, 1H), 2.29 (s, 3H), 2.19 (m, 1H), 2.15 (m, 1H), 2.10 (m, 1H), 1.96 (m, 1H), 1.80 (m, 2H), 1.53 (m, 1H), 1.36 (m, 1H), 1.24 (m, 1H).



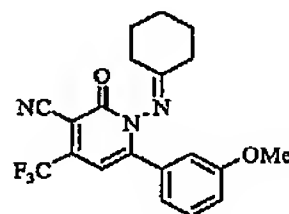
-167-

$^1\text{H-NMR}$ (CDCl_3): δ 7.33 – 7.24 (m, 4H), 6.48 (s, 1H), 2.49 (m, 1H), 2.42 (s, 3H), 2.38 (m, 1H), 2.19 (m, 1H), 2.04 (m, 1H), 1.87 (m, 2H), 1.59 (m, 2H), 1.49 (m, 1H), 1.36 (m, 1H).



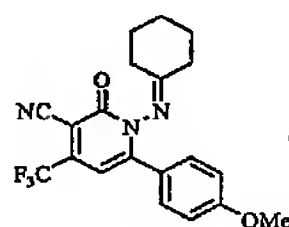
3.56

5 $^1\text{H-NMR}$ (CDCl_3): δ 7.47 (m, 1H), 7.16 (m, 1H), 7.05 (m, 1H), 6.95 (m, 1H), 6.45 (s, 1H), 3.79 (s, 3H), 2.40 (m, 1H), 2.22 (m, 2H), 2.06 (m, 1H), 1.91 (m, 1H), 1.81 (m, 1H), 1.58 (m, 2H), 1.46 (m, 2H).



3.57

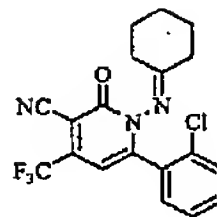
10 $^1\text{H-NMR}$ (CDCl_3): δ 7.37 (m, 1H), 7.03 (m, 1H), 6.95 (m, 1H), 6.93 (m, 1H), 6.50 (s, 1H), 3.84 (s, 3H), 2.49 (m, 1H), 2.38 (m, 1H), 2.18 (m, 1H), 2.05 (m, 1H), 1.86 (m, 2H), 1.60 (m, 2H), 1.49 (m, 1H), 1.37 (m, 1H).



3.58

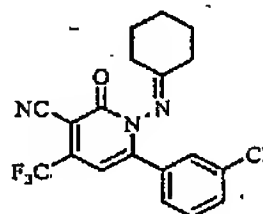
15 $^1\text{H-NMR}$ (CDCl_3): δ 7.39 (d, $J = 9.0$ Hz, 2H), 6.96 (d, $J = 9.0$ Hz, 2H), 6.48 (s, 1H), 3.87 (s, 3H), 2.52 (m, 1H), 2.41 (m, 1H), 2.18 (m, 1H), 2.02 (m, 1H), 1.87 (m, 2H), 1.60 (m, 2H), 1.52 (m, 1H), 1.34 (m, 1H).

-168-



3.59

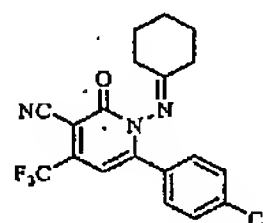
$^1\text{H-NMR}$ (CDCl_3): δ 7.57 – 7.30 (m, 4H), 6.46 (s, 1H), 2.37 (m, 1H), 2.23 (m, 2H), 2.05 (m, 1H), 1.91 (m, 1H), 1.83 (m, 1H), 1.60 (m, 2H), 1.54 (m, 1H), 1.44 (m, 1H).



3.60

5

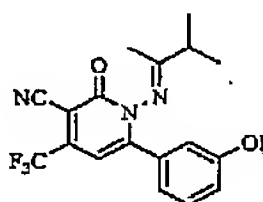
$^1\text{H-NMR}$ (CDCl_3): δ 7.50 (m, 1H), 7.43 (m, 1H), 7.37 (m, 1H), 7.31 (m, 1H), 6.49 (s, 1H), 2.48 (m, 1H), 2.40 (m, 1H), 2.22 (m, 1H), 2.11 (m, 1H), 1.92 (m, 2H), 1.63 (m, 2H), 1.51 (m, 1H), 1.42 (m, 1H).



3.61

10

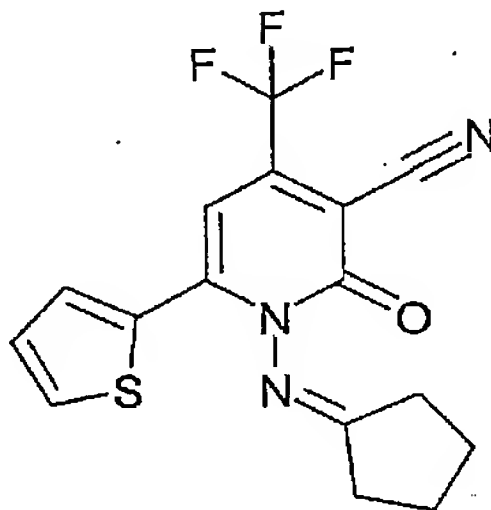
$^1\text{H-NMR}$ (CDCl_3): δ 7.46 (d, $J = 8.3$ Hz, 2H), 7.36 (d, $J = 8.3$ Hz, 2H), 6.47 (s, 1H), 2.49 (m, 1H), 2.38 (m, 1H), 2.19 (m, 1H), 2.02 (m, 1H), 1.88 (m, 2H), 1.61 (m, 2H), 1.51 (m, 1H), 1.37 (m, 1H).



3.62

-169-

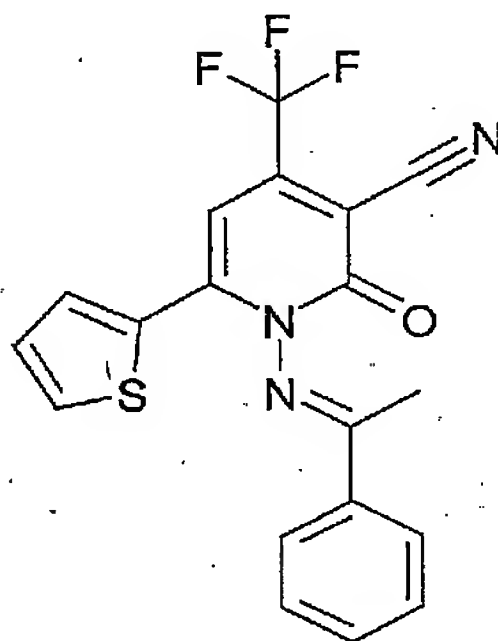
$^1\text{H-NMR}$ (CDCl_3): δ 7.31 (m, 1H), 6.98 (m, 1H), 6.95 (m, 1H), 2.08 (m, 1H), 6.53 (s, 1H), 2.62 (m, $J = 7.0$ Hz, 1H), 1.76 (s, 3H), 1.03 (d, $J = 7.0$ Hz, 3H), 0.99 (d, $J = 7.0$ Hz, 3H).



5

3.63

1-Cyclopentylideneamino-2-oxo-6-(thiophen-2-yl)-4-(trifluoromethyl)-1,2-dihydropyridine-3-carbonitrile
MS (ES⁺): 352.2 (M+H)

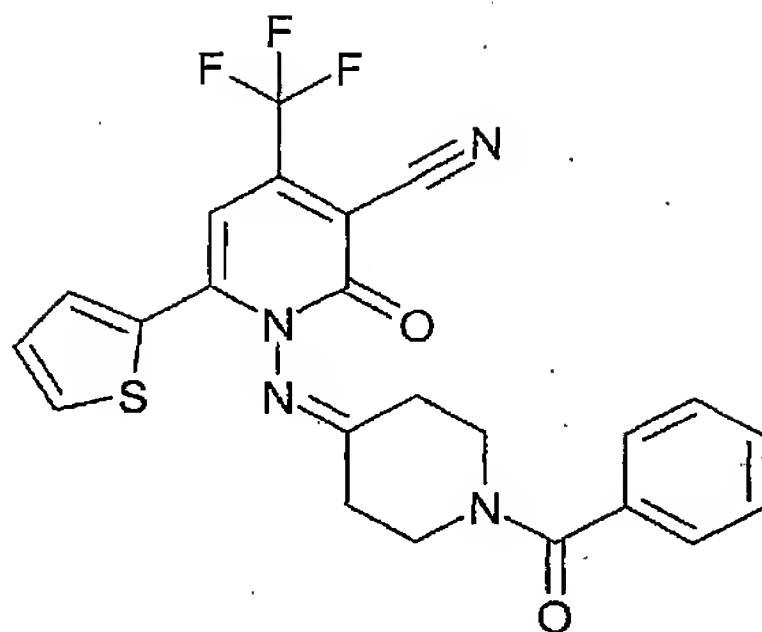


10

3.64

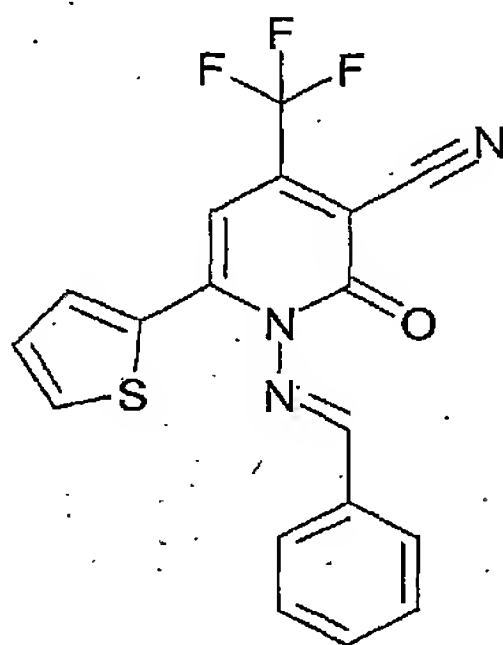
2-Oxo-1-(1-phenyl-ethylideneamino)-6-(thiophen-2-yl)-4-(trifluoromethyl)-1,2-dihydropyridine-3-carbonitrile
MS (ES⁺): 388.0 (M+H)

-170-



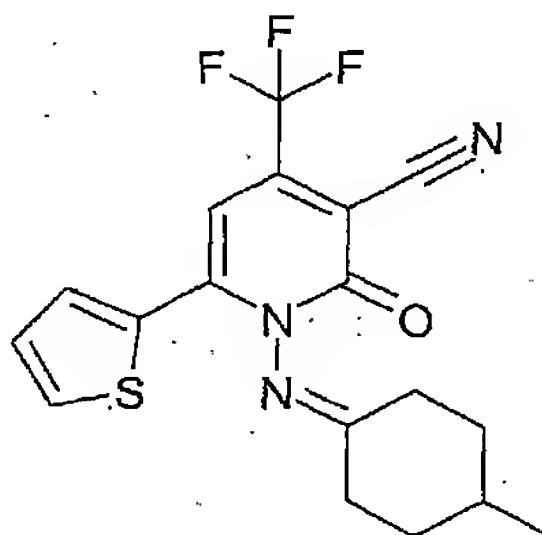
3.65

- 1-(1-Benzoyl-piperidin-4-ylideneamino)-2-oxo-6-thiophen-2-yl-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile
5 MS (ES+):471.3 (M+H)



3.66

- 1-(Benzylidene-amino)-2-oxo-6-thiophen-2-yl-4-trifluoromethyl-1,2-dihydro-
10 pyridine-3-carbonitrile
MS (ES+):374.1 (M+H)

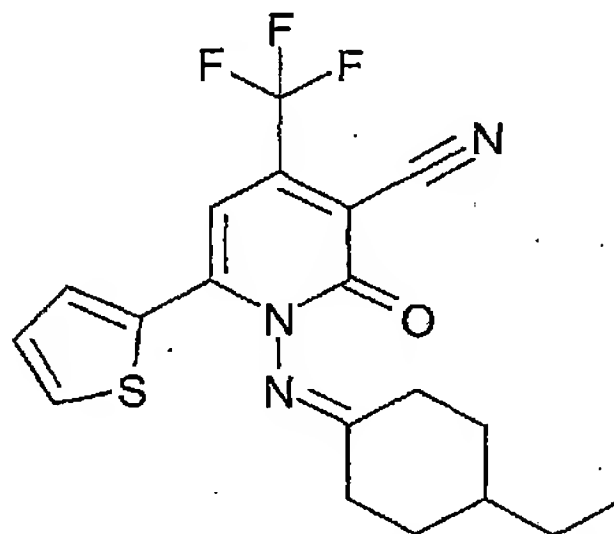


-171-

3.67

1-(4-Methyl-cyclohexylideneamino)-2-oxo-6-thiophen-2-yl-4-trifluoromethyl-
1,2-dihydro-pyridine-3-carbonitrile

MS (ES⁺):380.1 (M+H)

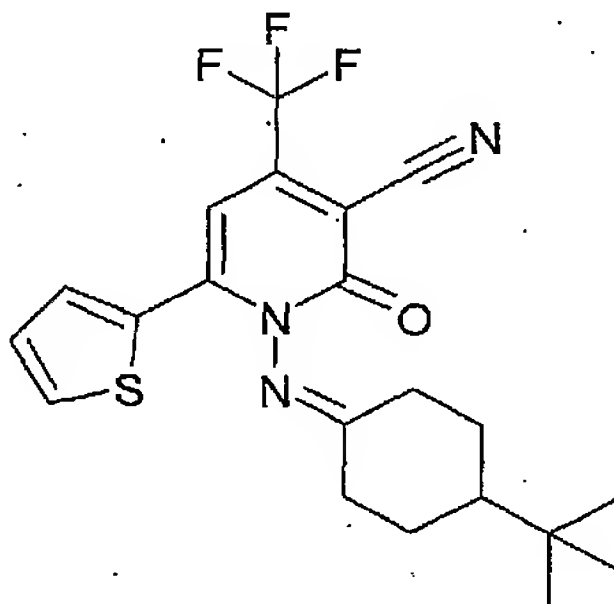


5

3.68

1-(4-Ethyl-cyclohexylideneamino)-2-oxo-6-thiophen-2-yl-4-trifluoromethyl-
1,2-dihydro-pyridine-3-carbonitrile

MS (ES⁺):394.0 (M+H)



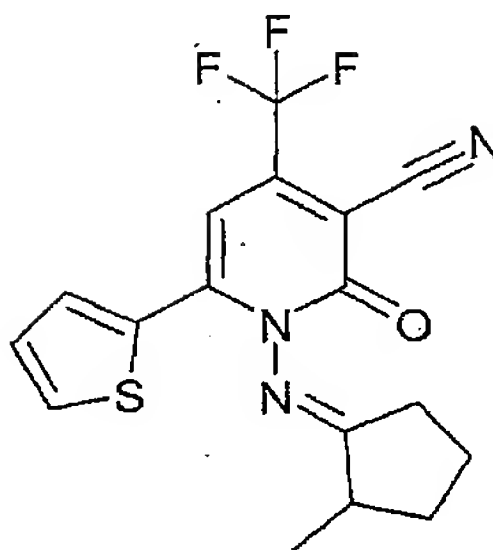
10

3.69

1-(4-tert-Butyl-cyclohexylideneamino)-2-oxo-6-thiophen-2-yl-4-
trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile

MS (ES⁺):422.0 (M+H)

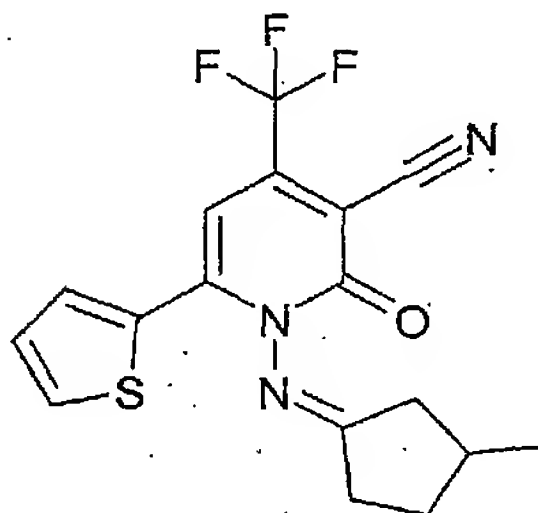
-172-



3.70

1-(2-Methyl-cyclopentylideneamino)-2-oxo-6-thiophen-2-yl-4-trifluoromethyl-
1,2-dihydro-pyridine-3-carbonitrile

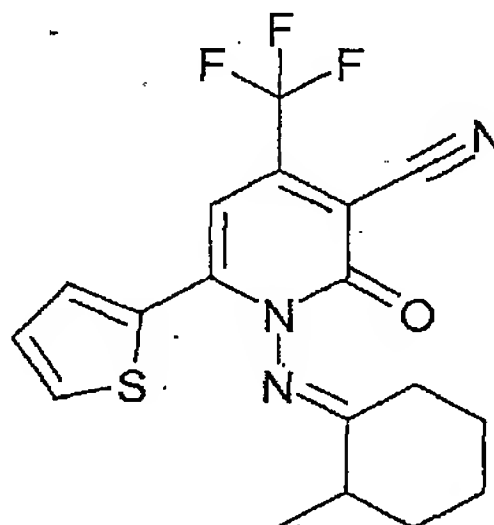
5 MS (ES+):366.1 (M+H)



3.71

1-(3-Methyl-cyclopentylideneamino)-2-oxo-6-thiophen-2-yl-4-trifluoromethyl-
1,2-dihydro-pyridine-3-carbonitrile

10 MS (ES+):366.2 (M+H)



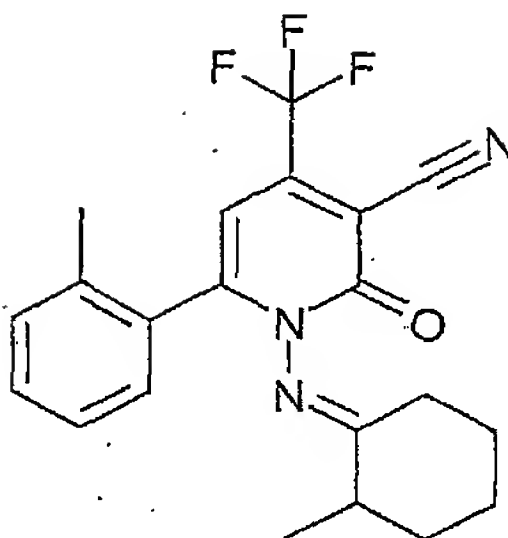
3.72

1-(2-Methyl-cyclohexylideneamino)-2-oxo-6-thiophen-2-yl-4-trifluoromethyl-
1,2-dihydro-pyridine-3-carbonitrile

15

MS (ES+):380.3 (M+H)

-173-



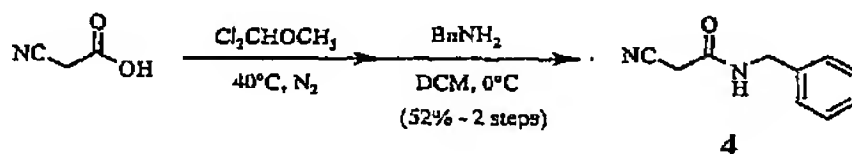
3.73

5 1-(2-Methyl-cyclohexylideneamino)-2-oxo-6-o-tolyl-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile
MS (ES⁺):388.2 (M+H)

EXAMPLE 4

10

This example illustrates the preparation of compound 4.



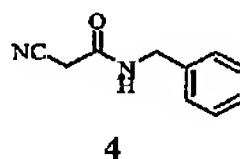
15

20

Cyanoacetic acid (8.0 g, 94.1 mmoles) and α,α -dichloromethyl methyl ether were measured out into a 30 mL round-bottom flask equipped with a magnetic stirbar. The flask was sealed with a septum, and the vessel was continuously flushed with dry N₂ gas. The temperature was carefully raised to 40 °C at which temperature the mixture began to liquify and bubble. Nitrogen flushing was maintained throughout this period with adequate venting to atmosphere to permit the release of gases formed during the reaction. The temperature was maintained at 40 °C for 45 minutes while adequate stirring was maintained by vigilant monitoring. After this period the nitrogen line was submerged into the stirring reaction mixture to facilitate the purging of gases (HCl) from the solution. The nitrogen purge was carried out

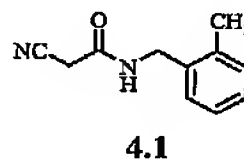
-174-

dissolved into 100 mL of anhydrous DCM. To the stirring acid chloride solution at 0 °C was slowly added benzylamine (21 mL, 192.2 mmoles) and the resulting mixture was stirred at ambient temperature for 30 min. After this period the reaction mixture was washed with 1N HCl (2 x 20 mL), sat'd NaHCO₃ (2 x 20 mL) and brine. The DCM solution was dried over anhydrous Na₂SO₄ and was evaporated *in vacuo* to yield the crude product as a yellowish solid. The crude material was purified by recrystallization in DCM/Hexane to yield 8.5 g (52% yield) of product as yellow, needlelike crystals. (Alternatively, the product can be purified using flash silica chromatography in 60% EtOAc/Hexane).

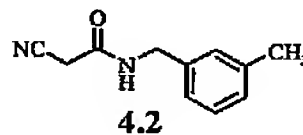


¹H-NMR (CDCl₃): δ 7.39-7.28 (m, 5H), 6.39 (bs, 1H), 4.48 (d, J=5.7Hz, 2H), 3.40 (s, 2H).

The following compounds were prepared in a manner similar to that described above.



¹H-NMR (CDCl₃): δ 7.25-7.19 (m, 4H), 6.15 (bs, 1H), 4.49 (d, J=5.4Hz, 2H), 3.41 (s, 2H), 2.34 (s, 3H).

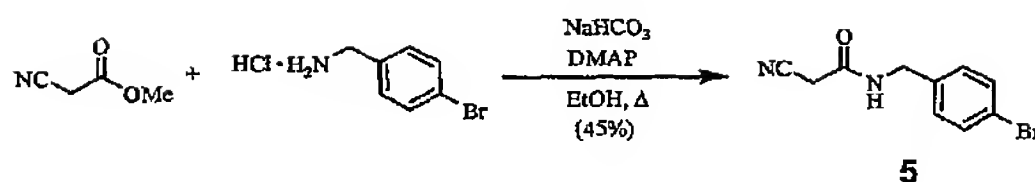


¹H-NMR (CDCl₃): δ 7.27-7.23 (m, 1H), 7.14-7.07 (m, 3H), 6.29 (bs, 1H), 4.45 (d, J=5.6Hz, 2H), 3.41 (s, 2H), 2.36 (s, 3H).

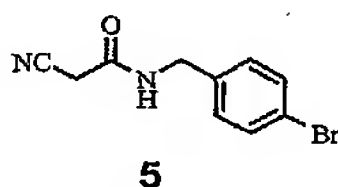
An alternative procedure utilizing commercially available methyl cyanoacetate illustrates the preparation of compound 4.

-175-

EXAMPLE 5

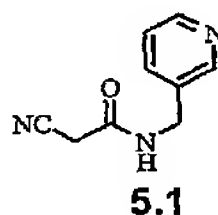


- Methyl cyanoacetate (0.8 mL, 9.1 mmol) and 4-bromobenzylammonium chloride (0.97 g, 4.4 mmol) were mixed with 10 mL of anhydrous ethanol within a round-bottom flask. To the stirring mixture at room temp was added sodium bicarbonate (0.55 g, 6.5 mmol) and 4-(dimethylamino)pyridine (0.25 g, 2.0 mmol). The mixture was then stirred at 80 °C for 5 hours. After this period the reaction was evaporated *in vacuo*, combined with DCM, and was washed with 1N HCl (2 x 15 mL), sat'd NaHCO_3 (2 x 15 mL) and brine. The DCM solution was dried over anhydrous Na_2SO_4 and was evaporated *in vacuo* to yield the crude product residue. The crude residue was purified using flash silica chromatography (60% EtOAc/Hexane) to yield 0.49 g (45% yield) of product as a yellow solid.



- $^1\text{H-NMR}$ (CDCl_3): δ 7.49 (d, $J=8.3\text{Hz}$, 2H), 7.17 (d, $J=8.3\text{Hz}$, 2H), 6.38 (bs, 1H), 4.44 (d, $J=5.8\text{Hz}$, 2H), 3.42 (s, 2H).

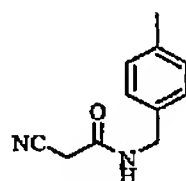
The following compounds were prepared in a manner similar to that described above.



2-Cyano-N-pyridin-3-ylmethyl-acetamide

-176-

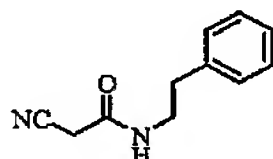
$^1\text{H-NMR}$ (CDCl_3): δ 8.53-8.48 (m, 2H), 7.65 (dt, $J'=7.8\text{Hz}$, $J''=1.8\text{Hz}$, 1H), 7.29 (dd, $J'=7.8\text{Hz}$, $J''=4.8\text{Hz}$, 1H), 7.25 (bs, 1H), 4.47 (d, $J=5.8\text{Hz}$, 2H), 3.43 (s, 2H).



5.2

2-Cyano-*N*-(4-methyl-benzyl)-acetamide

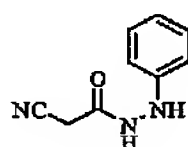
5 $^1\text{H-NMR}$ (CDCl_3): δ 7.18 (m, 4H), 6.27 (bs, 1H), 4.44 (d, $J=5.6\text{Hz}$, 2H), 3.40 (s, 2H), 2.35 (s, 3H).



5.3

2-Cyano-*N*-phenethyl-acetamide

$^1\text{H-NMR}$ (CDCl_3): δ 7.34 (m, 2H), 7.29-7.16 (m, 3H), 6.06 (bs, 1H), 3.58 (m, 2H), 3.32 (s, 2H), 2.86 (t, $J=7.1\text{Hz}$, 2H).

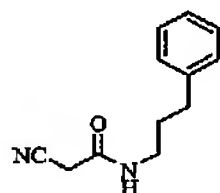


5.4

Cyano-acetic acid *N'*-phenyl-hydrazide

10

$^1\text{H-NMR}$ (CDCl_3): {rotamers} δ 7.93 (bs, 0.36H), 7.53-7.39 (m, 1.1H), 7.36-7.20 (m, 3.4H), 7.11-6.91 (m, 1.4H), 6.89-6.76 (m, 1.7H), 6.08 (m, 0.40H), 5.92 (m, 0.50H), 4.88 (m, 0.25H), 4.44 (m, 0.33H), 3.90 (s, 0.50H), 3.60 (s, 1H), 3.48 (s, 1H), 3.33 (s, 0.25H).



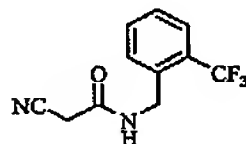
5.5

2-Cyano-*N*-(3-phenyl-propyl)-acetamide

15

-177-

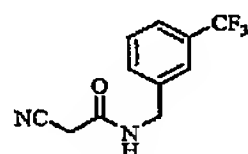
$^1\text{H-NMR}$ (CDCl_3): δ 7.34-7.27 (m, 2H), 7.24-7.14 (m, 3H), 6.07 (bs, 1H), 3.34 (bq, $J=5.1\text{Hz}$, 2H), 3.30 (s, 2H), 2.68 (bt, $J=7.5\text{Hz}$, 2H), 1.90 (m, $J=7.5\text{Hz}$, 2H).



5.6

2-Cyano-*N*-(2-trifluoromethylbenzyl)-acetamide

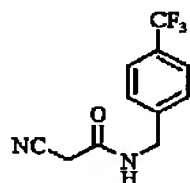
5 $^1\text{H-NMR}$ (CDCl_3): δ 7.69 (bd, $J=7.8\text{Hz}$, 1H), 7.59-7.53 (m, 2H), 7.48-7.41 (m, 1H), 6.40 (bs, 1H), 4.67 (d, $J=6.1\text{Hz}$, 2H), 3.40 (s, 2H).



5.7

2-Cyano-*N*-(3-trifluoromethylbenzyl)-acetamide

$^1\text{H-NMR}$ (CDCl_3): δ 7.62-7.47 (m, 4H), 6.49 (bs, 1H), 4.55 (d, $J=5.8\text{Hz}$, 2H), 3.44 (s, 2H).

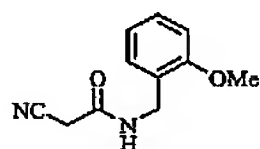


5.8

2-Cyano-*N*-(4-trifluoromethylbenzyl)-acetamide

10

$^1\text{H-NMR}$ (CDCl_3): δ 7.62 (d, $J=8.1\text{Hz}$, 2H), 7.42 (d, $J=8.1\text{Hz}$, 2H), 6.48 (bs, 1H), 4.55 (d, $J=6.1\text{Hz}$, 2H), 3.44 (s, 2H).

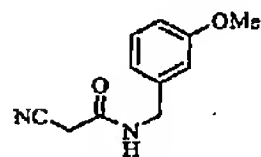


5.9

2-Cyano-*N*-(2-methoxybenzyl)-acetamide

-178-

$^1\text{H-NMR}$ (CDCl_3): δ 7.35-7.23 (m, 2H), 6.97-6.89 (m, 2H), 6.80 (bs, 1H), 4.48 (d, $J=5.8\text{Hz}$, 2H), 3.89 (s, 3H), 3.34 (s, 2H).

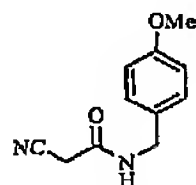


5.10

2-Cyano-N-(3-methoxybenzyl)-acetamide

$^1\text{H-NMR}$ (CDCl_3): δ 7.30-7.25 (m, 1H), 6.89-6.81 (m, 3H), 6.36 (bs, 1H), 4.45 (d, $J=5.8\text{Hz}$, 2H), 3.81 (s, 3H), 3.40 (s, 2H).

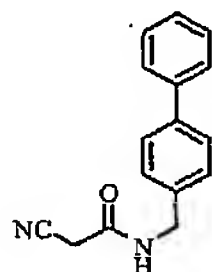
5



5.11

2-Cyano-N-(4-methoxybenzyl)-acetamide

$^1\text{H-NMR}$ (CDCl_3): δ 7.22 (d, $J=8.6\text{Hz}$, 2H), 6.89 (d, $J=8.6\text{Hz}$, 2H), 6.26 (bs, 1H), 4.42 (d, $J=5.3\text{Hz}$, 2H), 3.81 (s, 3H), 3.40 (s, 2H).

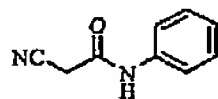


5.12

N-Biphenyl-4-ylmethyl-2-cyanoacetamide

$^1\text{H-NMR}$ (CDCl_3): δ 7.62-7.55 (m, 4H), 7.48-7.42 (m, 2H), 7.40-7.33 (m, 3H), 6.40 (bs, 1H), 4.53 (d, $J=5.8\text{Hz}$, 2H), 3.43 (s, 2H).

10

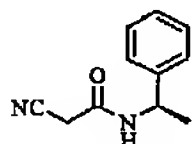


5.13

2-Cyano-N-phenylacetamide

-179-

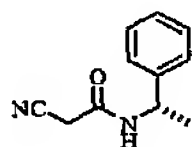
$^1\text{H-NMR}$ (CDCl_3): δ 7.66 (bs, 1H), 7.53-7.48 (m, 2H), 7.41-7.35 (m, 2H), 7.23-7.18 (m, 1H), 3.57 (s, 2H).



5.14

2-Cyano-*N*-(1-phenyl-ethyl)-
acetamide

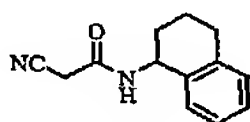
5 $^1\text{H-NMR}$ (CDCl_3): δ 7.41-7.23 (m, 5H), 6.24 (bs, 1H), 5.12 (m, 1H), 3.37 (m, 2H), 1.55 (d, $J=7.1\text{Hz}$, 3H).



5.15

2-Cyano-*N*-(1-phenyl-ethyl)-
acetamide

$^1\text{H-NMR}$ (CDCl_3): δ 7.41-7.23 (m, 5H), 6.24 (bs, 1H), 5.12 (m, 1H), 3.37 (m, 2H), 1.55 (d, $J=7.1\text{Hz}$, 3H).



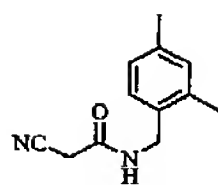
5.16

2-Cyano-*N*-(1,2,3,4-tetrahydro-
naphthalen-1-yl)-acetamide

10

$^1\text{H-NMR}$ (CDCl_3): δ 7.28-7.09 (m, 4H), 6.26 (bs, 2H), 5.22-5.14 (m, 1H), 3.40 (s, 2H), 2.90-2.71 (m, 2H), 2.12-2.00 (m, 1H), 1.93-1.77 (m, 3H).

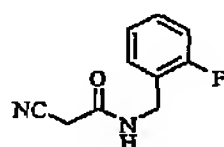
-180-



5.17

2-Cyano-N-(2,4-dimethylbenzyl)-acetamide

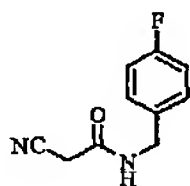
$^1\text{H-NMR}$ (CDCl_3): δ 7.14-7.08 (m, 1H), 7.05-6.98 (m, 2H), 6.13 (bs, 1H), 4.44 (d, $J=5.3\text{Hz}$, 2H), 3.38 (s, 2H), 2.32 (s, 3H), 2.30 (s, 3H).



5.18

2-Cyano-N-(2-fluorobenzyl)-acetamide

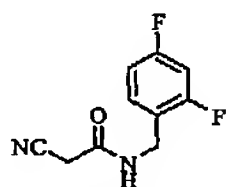
5 $^1\text{H-NMR}$ (CDCl_3): δ 7.40-7.27 (m, 2H), 7.16-7.05 (m, 2H), 6.45 (bs, 1H), 4.54 (d, $J=5.8\text{Hz}$, 2H), 3.39 (s, 2H).



5.19

2-Cyano-N-(4-fluorobenzyl)-acetamide

$^1\text{H-NMR}$ (CDCl_3): δ 7.30-7.23 (m, 2H), 7.08-7.00 (m, 2H), 6.40 (bs, 1H), 4.45 (d, $J=5.8\text{Hz}$, 2H), 3.41 (s, 2H).

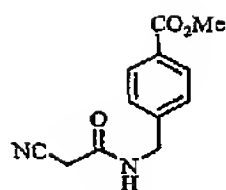


5.20

10 2-Cyano-N-(2,4-difluorobenzyl)-acetamide

$^1\text{H-NMR}$ (CDCl_3): δ 7.38-7.29 (m, 1H), 6.90-6.80 (m, 2H), 6.51 (bs, 1H), 4.48 (d, $J=6.1\text{Hz}$, 2H), 3.39 (s, 2H).

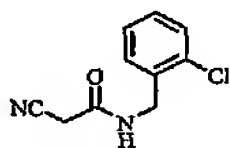
-181-



5.21

4-[(2-Cyano-acetylamino)-methyl]-
benzoic acid methyl ester

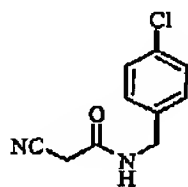
$^1\text{H-NMR}$ (CDCl_3): δ 8.03 (d, $J=8.1\text{Hz}$, 2H), 7.36 (d, $J=8.1\text{Hz}$, 2H), 6.46 (bs, 1H), 4.55 (d, $J=5.8\text{Hz}$, 2H), 3.92 (s, 3H), 3.45 (s, 2H).



5.22

N-(2-Chloro-benzyl)-2-cyano-acetamide

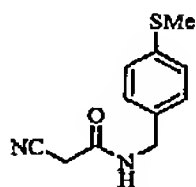
5 $^1\text{H-NMR}$ (CDCl_3): δ 7.43-7.36 (m, 2H), 7.31-7.23 (m, 2H), 6.53 (bs, 1H), 4.58 (d, $J=5.8\text{Hz}$, 2H), 3.40 (s, 2H).



5.23

N-(4-Chloro-benzyl)-2-cyano-acetamide

$^1\text{H-NMR}$ (CDCl_3): δ 7.36-7.30 (d, $J=8.6\text{Hz}$, 2H), 7.25-7.20 (d, $J=8.6\text{Hz}$, 2H), 6.43 (bs, 1H), 4.45 (d, $J=5.81\text{Hz}$, 2H), 3.42 (s, 2H).



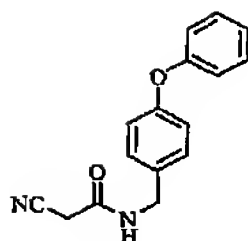
5.24

2-Cyano-*N*-(4-methylsulfanyl)-
benzyl)-acetamide

10

$^1\text{H-NMR}$ (CDCl_3): δ 7.26-7.18 (m, 4H), 6.34 (bs, 1H), 4.43 (d, $J=5.6\text{Hz}$, 2H), 3.40 (s, 2H), 2.48 (s, 3H).

-182-

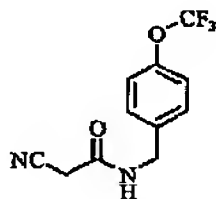


5.25

2-Cyano-N-(4-phenoxy-benzyl)-acetamide

¹H-NMR (CDCl₃): δ 7.38-7.32 (m, 2H), 7.28-7.23 (m, 3H), 7.16-7.09 (m, 1H), 7.04-6.96 (m, 4H), 6.35 (bs, 1H), 4.45 (d, J=5.6Hz, 2H), 3.42 (s, 2H).

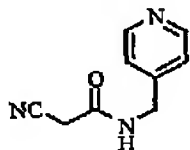
5



5.26

2-Cyano-N-(4-trifluoromethoxy-benzyl)-acetamide

¹H-NMR (CDCl₃): δ 7.36-7.29 (m, 2H), 7.23-7.17 (m, 2H), 6.46 (bs, 1H), 4.48 (d, J=5.8Hz, 2H), 3.42 (s, 2H).

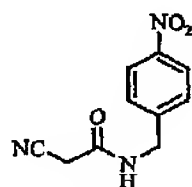


5.27

2-Cyano-N-pyridin-4-ylmethyl-acetamide

¹H-NMR (CDCl₃): δ 8.61-8.51 (m, 2H), 7.24-7.18 (m, 2H), 6.99 (bs, 1H), 4.49 (d, J=5.8Hz, 2H), 3.48 (s, 2H).

10

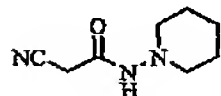


5.28

2-Cyano-N-(4-nitro-benzyl)-acetamide

-183-

$^1\text{H-NMR}$ (CDCl_3): δ 8.23 (d, $J=8.6\text{Hz}$, 2H), 7.47 (d, $J=8.6\text{Hz}$, 2H), 6.55 (bs, 1H), 4.60 (d, $J=6.1\text{Hz}$, 2H), 3.47 (s, 2H).

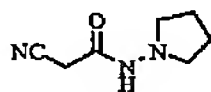


5.29

2-Cyano-*N*-piperidin-1-yl-acetamide

$^1\text{H-NMR}$ (CDCl_3): δ 6.51 (bs, 1H), 3.54 (s, 2H), 3.16-3.04 (m, 2H), 2.43-2.29 (m, 2H) 1.81-1.54 (m, 6H).

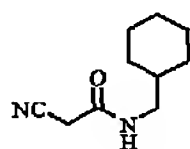
5



5.30

2-Cyano-*N*-pyrrolidin-1-yl-acetamide

$^1\text{H-NMR}$ (CDCl_3): δ 6.85 (bs, 1H), 3.59 (s, 2H), 3.46-3.03 (bm, 2H), 2.78-2.22 (bm, 2H), 1.96-1.78 (m, 4H).

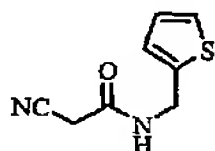


5.31

2-Cyano-*N*-cyclohexylmethyl-acetamide

10

$^1\text{H-NMR}$ (CDCl_3): δ 6.20 (bs, 1H), 3.38 (s, 2H), 3.15 (bt, $J=6.3\text{Hz}$, 2H), 1.79-1.68 (m, 5H), 1.58-1.44 (m, 1H), 1.36-1.09 (m, 3H), 1.02-0.86 (m, 2H).

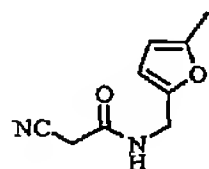


5.32

2-Cyano-*N*-thiophen-2-ylmethyl-acetamide

-184-

$^1\text{H-NMR}$ (CDCl_3): δ 7.26 (dd, $J'=5.1\text{Hz}$, $J''=1.3\text{Hz}$, 1H), 7.03-6.99 (m, 1H), 6.99-6.95 (m, 1H), 6.57 (bs, 1H), 4.64 (d, $J=5.6\text{Hz}$, 2H), 3.39 (s, 2H).

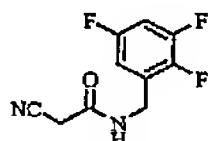


5.33

2-Cyano-*N*-(5-methyl-furan-2-ylmethyl)-acetamide

5

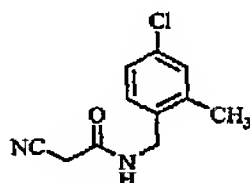
$^1\text{H-NMR}$ (CDCl_3): δ 6.52 (bs, 1H), 6.14 (d, $J=3.0\text{Hz}$, 1H), 5.93-5.88 (m, 1H), 4.40 (d, $J=5.3\text{Hz}$, 2H), 3.39 (s, 2H), 2.27 (s, 3H).



5.34

2-Cyano-*N*-(2,3,5-trifluorobenzyl)-acetamide

$^1\text{H-NMR}$ (CDCl_3): δ 6.94-6.83 (m, 2H), 6.66 (bs, 1H), 4.53 (bd, $J=6.1\text{Hz}$, 2H), 3.44 (s, 2H).

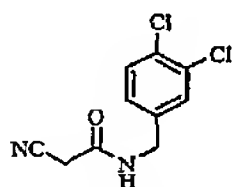


5.35

N-(4-Chloro-2-methylbenzyl)-2-cyanoacetamide

10

$^1\text{H-NMR}$ (CDCl_3): δ 7.22-7.13 (m, 3H), 6.28 (bs, 1H), 4.43 (d, $J=5.6\text{Hz}$, 2H), 3.40 (s, 2H), 2.31 (s, 3H).

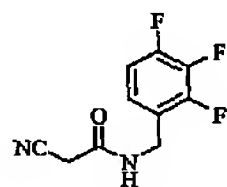


5.36

2-Cyano-*N*-(3,4-dichlorobenzyl)-acetamide

-185-

$^1\text{H-NMR}$ (CDCl_3): δ 8.37 (bs, 1H), 7.14-7.09 (m, 2H), 6.87 (dd, $J'=8.1\text{Hz}$, $J''=2.0\text{Hz}$, 1H), 4.02 (d, $J=5.8\text{Hz}$, 2H), 3.20 (s, 2H).

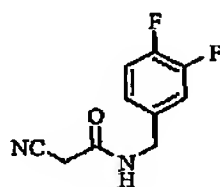


5.37

2-Cyano-*N*-(2,3,4-trifluoro-benzyl)-acetamide

5

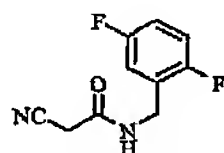
$^1\text{H-NMR}$ (CDCl_3): δ 7.14-7.06 (m, 1H), 7.01-6.90 (m, 1H), 6.54 (bs, 1H), 4.51 (d, $J=5.8\text{Hz}$, 2H), 3.41 (s, 2H).



5.38

2-Cyano-*N*-(3,4-difluoro-benzyl)-acetamide

$^1\text{H-NMR}$ (CDCl_3): δ 7.19-7.08 (m, 2H), 7.06-6.98 (m, 1H), 6.46 (bs, 1H), 4.44 (d, $J=5.8\text{Hz}$, 2H), 3.43 (s, 2H).

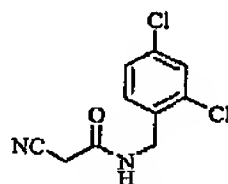


5.39

2-Cyano-*N*-(2,5-difluoro-benzyl)-acetamide

10

$^1\text{H-NMR}$ (CDCl_3): δ 7.09-6.94 (m, 3H), 6.58 (bs, 1H), 4.50 (d, $J=6.1\text{Hz}$, 2H), 3.42 (s, 2H).

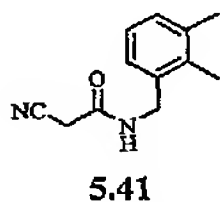


5.40

2-Cyano-*N*-(2,4-dichloro-benzyl)-acetamide

-186-

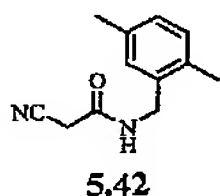
$^1\text{H-NMR}$ (CDCl_3): δ 7.42 (d, $J=2.0\text{Hz}$, 1H), 7.35-7.23 (m, 2H), 6.58 (bs, 1H), 4.53 (d, $J=6.1\text{Hz}$, 2H), 3.40 (s, 2H).



2-Cyano-*N*-(2,3-dimethyl-benzyl)-acetamide

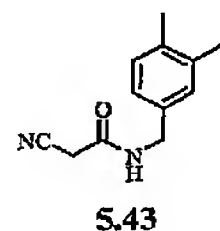
5

$^1\text{H-NMR}$ (CDCl_3): δ 7.18-7.06 (m, 3H), 6.18 (bs, 1H), 4.49 (d, $J=5.3\text{Hz}$, 2H), 3.37 (s, 2H), 2.30 (s, 3H), 2.22 (s, 3H).



2-Cyano-*N*-(2,5-dimethyl-benzyl)-acetamide

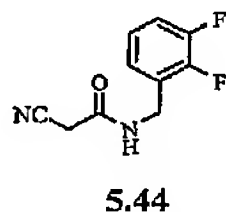
$^1\text{H-NMR}$ (CDCl_3): δ 7.11-7.01 (m, 3H), 6.16 (bs, 1H), 4.44 (d, $J=5.3\text{Hz}$, 2H), 3.40 (d, 2H), 2.32 (s, 3H), 2.29 (s, 3H).



2-Cyano-*N*-(3,4-dimethyl-benzyl)-acetamide

10

$^1\text{H-NMR}$ (CDCl_3): δ 7.12 (d, $J=7.6\text{Hz}$, 1H), 7.05 (bs, 1H), 7.01 (dd, $J'=7.6\text{Hz}$, $J''=1.3\text{Hz}$, 1H), 6.34 (bs, 1H), 4.40 (d, $J=5.8\text{Hz}$, 2H), 3.38 (d, 2H), 2.26 (s, 3H), 2.25 (s, 3H).

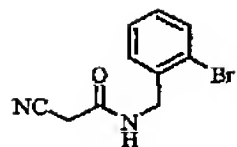


2-Cyano-*N*-(2,3-difluoro-benzyl)-acetamide

15

$^1\text{H-NMR}$ (CDCl_3): δ 7.19-7.0 (m, 3H), 6.46 (bs, 1H), 4.56 (dd, $J'=6.1\text{Hz}$, $J''=0.8\text{Hz}$, 2H), 3.41 (s, 2H).

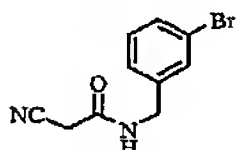
-187-



5.45

N-(2-Bromo-benzyl)-2-cyano-acetamide

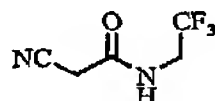
$^1\text{H-NMR}$ (CDCl_3): δ 7.48-7.41 (m, 2H), 7.25-7.19 (m, 2H), 6.45 (bs, 1H), 4.45 (d, $J=5.8\text{Hz}$, 2H), 3.43 (s, 2H).



5.46

N-(3-Bromo-benzyl)-2-cyano-acetamide

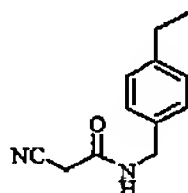
- 5 $^1\text{H-NMR}$ (CDCl_3): δ 7.58 (dd, $J'=8.1\text{Hz}$, $J''=1.0\text{Hz}$, 1H), 7.39 (dd, $J'=7.8\text{Hz}$, $J''=1.5\text{Hz}$, 1H), 7.31 (dt, $J'=7.6\text{Hz}$, $J''=1.0\text{Hz}$, 1H), 7.20 (dt, $J'=7.6\text{Hz}$, $J''=1.5\text{Hz}$, 1H), 6.59 (bs, 1H), 4.56 (d, $J=5.8\text{Hz}$, 2H), 3.39 (s, 2H).



5.47

2-Cyano-*N*-(2,2,2-trifluoro-ethyl)-acetamide

- 10 $^1\text{H-NMR}$ (CDCl_3): δ 6.38 (bs, 1H), 3.98 (m, 2H), 3.48 (s, 2H).

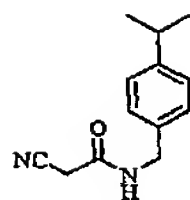


5.48

2-Cyano-*N*-(4-ethyl-benzyl)-acetamide

$^1\text{H-NMR}$ (CDCl_3): δ 7.23-7.16 (m, 4H), 6.47 (bs, 1H), 4.42 (d, $J=5.6\text{Hz}$, 2H), 3.36 (s, 2H), 2.64 (q, $J=7.6\text{Hz}$, 2H), 1.23 (t, $J=7.6\text{Hz}$, 3H).

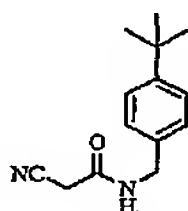
-188-



5.49

2-Cyano-N-(4-isopropylbenzyl)-acetamide

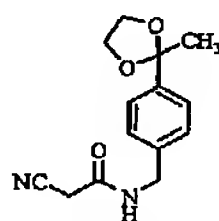
$^1\text{H-NMR}$ (CDCl_3): δ 7.23-7.16 (m, 4H), 6.65 (bs, 1H), 4.39 (d, $J=5.6\text{Hz}$, 2H), 3.33 (s, 2H), 2.90 (m, $J=6.8\text{Hz}$, 1H), 1.24 (d, $J=6.8\text{Hz}$, 6H).



5.50

N-(4-*tert*-Butylbenzyl)-2-cyanoacetamide

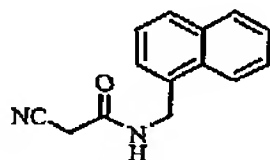
5 $^1\text{H-NMR}$ (CDCl_3): δ 7.37 (d, $J=8.3\text{Hz}$, 2H), 7.21 (d, $J=8.3\text{Hz}$, 2H), 6.59 (bs, 1H), 4.40 (d, $J=5.6\text{Hz}$, 2H), 3.33 (s, 2H), 1.31 (s, 9H).



5.51

2-Cyano-N-[4-(2-methyl-[1,3]dioxolan-2-yl)benzyl]-acetamide

10 $^1\text{H-NMR}$ (CDCl_3): δ 7.48 (d, $J=8.1\text{Hz}$, 2H), 7.27 (d, $J=8.1\text{Hz}$, 2H), 6.37 (bs, 1H), 4.47 (d, $J=5.6\text{Hz}$, 2H), 4.04 (m, 2H), 3.77 (m, 2H), 3.41 (s, 2H), 1.65 (s, 3H).

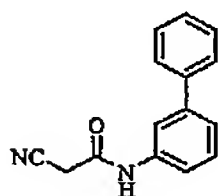


5.52

2-Cyano-N-naphthalen-1-ylmethylacetamide

-189-

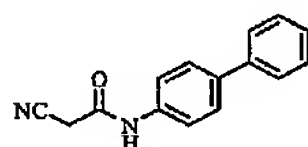
$^1\text{H-NMR}$ (CDCl_3): δ 7.98-7.83 (m, 3H), 7.61-7.50 (m, 2H), 7.48-7.41 (m, 2H), 6.27 (bs, 1H), 4.94 (d, $J=5.3\text{Hz}$, 2H), 3.39 (s, 2H).



5.53

N-Biphenyl-3-yl-2-cyano-acetamide

$^1\text{H-NMR}$ (CDCl_3): δ 7.75-7.33 (m, 10H), 3.59 (s, 2H).

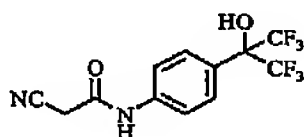


5.54

5

N-Biphenyl-4-yl-2-cyano-acetamide

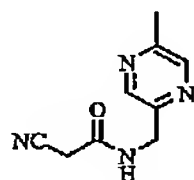
$^1\text{H-NMR}$ (CDCl_3): δ 7.74-7.67 (bs, 1H), 7.63-7.55 (m, 6H), 7.44 (t, $J=7.3\text{Hz}$, 2H), 7.38-7.32 (m, 1H), 3.59 (s, 2H).



5.55

2-Cyano-*N*-[4-(2,2,2-trifluoro-1-hydroxy-1-trifluoromethyl-ethyl)-phenyl]-acetamide

10 $^1\text{H-NMR}$ (CDCl_3): δ 9.59 (bs, 1H), 7.68-7.55 (m, 4H), 3.75 (s, 2H).

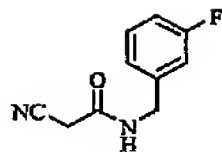


5.56

2-Cyano-*N*-(5-methyl-pyrazin-2-ylmethyl)-acetamide

$^1\text{H-NMR}$ (CDCl_3): δ 8.48 (s, 1H), 8.42 (s, 1H), 7.16 (bs, 1H), 4.61 (d, $J=5.1\text{Hz}$, 2H), 3.45 (s, 2H), 2.58 (s, 3H).

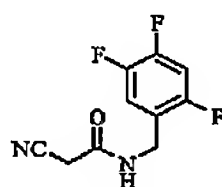
-190-



5.57

2-Cyano-N-(3-fluoro-benzyl)-
acetamide

$^1\text{H-NMR}$ (CDCl_3): δ 7.36-7.29 (m, 1H), 7.10-6.97 (m, 3H), 6.54 (bs, 1H),
4.47 (d, $J=5.8\text{Hz}$, 2H), 3.43 (s, 2H).



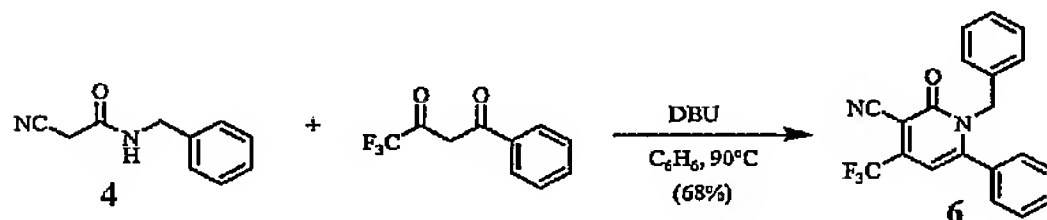
5.58

2-Cyano-N-(2,4,5-trifluoro-benzyl)-acetamide

5 $^1\text{H-NMR}$ (CDCl_3): 7.25-7.17 (m, 1H), 7.00-6.92 (m, 1H), 6.50 (bs, 1H),
4.47 (d, $J=6.1\text{Hz}$, 2H), 3.41 (s, 2H).

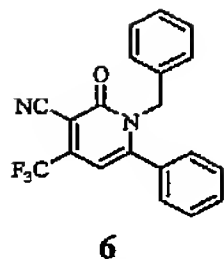
EXAMPLE 6

This example illustrates the preparation of compound 6.



10 Benzyl cyanoacetamide (0.2 g, 1.2 mmoles) was combined with 4,4,4-
trifluoro-1-phenyl-1,3-butanedione (0.24 g, 1.2 mmoles) and 1,8-
diazabicyclo[5.4.0]undec-7-ene (90 μL , 0.6 mmoles) in 2.5 mL of benzene.
The mixture was stirred at 90 $^{\circ}\text{C}$ for 12 hours. After this period the reaction
mixture was evaporated *in vacuo* and the residue was purified directly using
15 flask silica chromatography (20% EtOAc/Hexane) to yield 289 mg (68% yield)
of product 6 as a white solid.

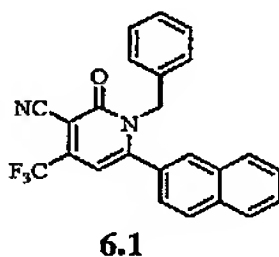
-191-



1-Benzyl-2-oxo-6-phenyl-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile

$^1\text{H-NMR}$ (CDCl_3): δ 7.54 (t, $J=7.6\text{Hz}$, 1H), 7.45 (t, $J=8\text{Hz}$, 2H), 7.25-7.17 (m, 5H), 6.88 (dd, $J'=6.9\text{Hz}$, $J''=1.5\text{Hz}$, 2H), 6.39 (s, 1H), 5.26 (s, 2H). MS (ES $^+$): 355.2 (M+H).

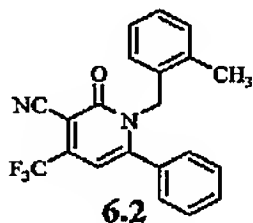
5 The following compounds were prepared in a manner similar to that described above.



1-Benzyl-6-naphthalen-2-yl-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile

$^1\text{H-NMR}$ (CDCl_3): δ 7.92 (d, $J=8.3\text{Hz}$, 2H), 7.77 (d, $J=8.2\text{Hz}$, 1H), 7.65-7.57 (m, 3H), 7.24-7.18 (m, 4H), 6.88 (d, $J=8.2\text{Hz}$, 2H), 6.49 (s, 1H), 5.29 (s, 2H).

10

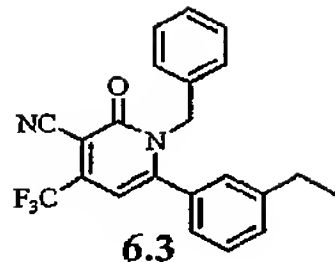


1-(2-Methyl-benzyl)-2-oxo-6-phenyl-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile

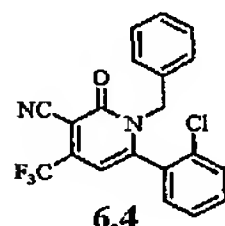
$^1\text{H-NMR}$ (CDCl_3): δ 7.49 (t, $J=7.4\text{Hz}$, 1H), 7.36 (t, $J=7.8\text{Hz}$, 2H), 7.16-7.05 (m, 5H), 6.74-6.72 (m, 1H), 6.45 (s, 1H), 5.15 (s, 2H), 1.93 (s, 3H).

15 MS(ES $^+$): 369.0 (M+H)

-192-

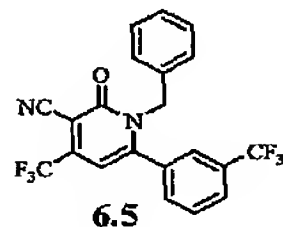


$^1\text{H-NMR}$ (CDCl_3): δ 7.36 (m, 2H), 7.24 (m, 3H), 7.03 (m, 1H), 6.92 (m, 1H), 6.90 (m, 1H), 6.88 (m, 1H), 6.40 (s, 1H), 5.25 (s, 2H), 2.60 (q, $J = 7.7$ Hz, 2H), 1.15 (t, $J = 7.7$ Hz, 3H).



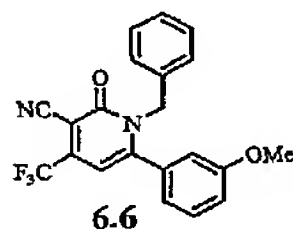
5

$^1\text{H-NMR}$ (CDCl_3): δ 7.53 (m, 1H), 7.50 (m, 1H), 7.28 (m, 1H), 7.21 (m, 1H), 7.18 (m, 2H), 6.97 (m, 1H), 6.84 (m, 1H), 6.82 (m, 1H), 6.35 (s, 1H), 5.68 (d, $J = 14.6$ Hz, 2H), 4.68 (d, $J = 14.6$ Hz, 2H).



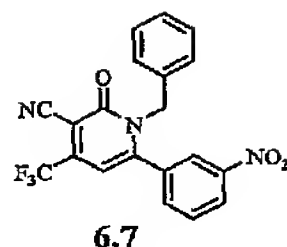
10

$^1\text{H-NMR}$ (CDCl_3): δ 7.80 (m, 1H), 7.60 (m, 1H), 7.38 (m, 1H), 7.32 (s, 1H), 7.24 (m, 3H), 6.81 (m, 2H), 6.39 (s, 1H), 5.21 (s, 2H).

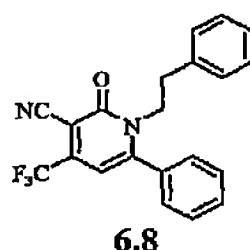


$^1\text{H-NMR}$ (CDCl_3): δ 7.36 (m, 1H), 7.25 (m, 3H), 7.05 (m, 1H), 6.92 (m, 2H), 6.79 (m, 1H), 6.60 (m, 1H), 6.42 (s, 1H), 5.25 (s, 2H), 3.64 (s, 3H).

-193-

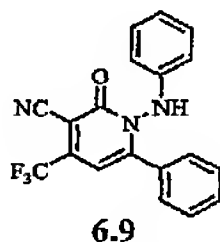


$^1\text{H-NMR}$ (CDCl_3): δ 8.38 (m, 1H), 7.97 (m, 1H), 7.65 (m, 1H), 7.48 (m, 1H), 7.25 (m, 3H), 6.81 (m, 2H), 6.40 (s, 1H), 5.23 (s, 2H).



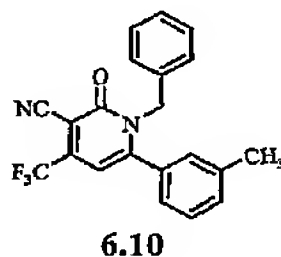
2-Oxo-1-phenethyl-6-phenyl-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile

5 $^1\text{H-NMR}$ (CDCl_3): δ 7.60-7.54 (m, 1H), 7.53-7.47 (m, 2H), 7.23-7.18 (m, 3H), 7.16-7.11 (m, 2H), 6.88-6.82 (m, 2H), 6.33 (s, 1H), 4.22-4.16 (m, 2H), 2.95-2.89 (m, 2H). MS(ES⁺): 368.7 (M+H)



2-Oxo-6-phenyl-1-phenylamino-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile

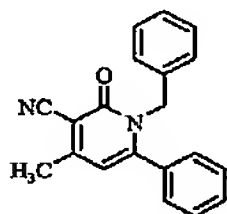
10 $^1\text{H-NMR}$ (CDCl_3): δ 7.59-7.54 (m, 2H), 7.53 (bs, 1H), 7.5-7.44 (m, 1H), 7.43-7.38 (m, 2H), 7.21-7.15 (m, 2H), 7.01-6.96 (m, 1H), 6.60 (d, $J=7.1\text{Hz}$, 2H), 6.59 (s, 1H). MS(ES⁺): 356.0 (M+H)



1-Benzyl-2-oxo-6-*m*-tolyl-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile

-194-

$^1\text{H-NMR}$ (CDCl_3): δ 7.34 (d, $J=5.1\text{Hz}$, 2H), 7.25-7.22 (m, 4H), 7.02-6.96 (m, 1H), 6.92-6.87 (m, 3H), 6.39 (s, 1H), 5.24 (bs, 2H), 2.32 (s, 3H). MS(ES⁺): 368.9 (M+H)

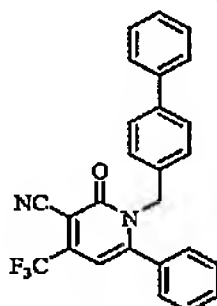


6.11

1-Benzyl-4-methyl-2-oxo-6-phenyl-1,2-dihydro-pyridine-3-carbonitrile

5

$^1\text{H-NMR}$ (CDCl_3): δ 7.50-7.44 (m, 1H), 7.38 (t, $J=8.1\text{Hz}$, 2H), 7.24-7.17 (m, 3H), 7.11 (d, $J=7.3\text{Hz}$, 2H), 6.91-6.83 (m, 2H), 6.08 (s, 1H), 5.17 (bs, 2H), 2.47 (s, 3H).

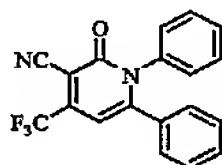


6.12

1-Biphenyl-4-ylmethyl-2-oxo-6-phenyl-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile

10

$^1\text{H-NMR}$ (CDCl_3): δ 7.59-7.51 (m, 3H), 7.51-7.40 (m, 6H), 7.38-7.32 (m, 1H), 7.23 (d, $J=6.8\text{Hz}$, 2H), 6.97 (d, $J=8.1\text{Hz}$, 2H), 6.42 (s, 1H), 5.30 (s, 2H). MS (ES⁺): 453.0 (M+Na).

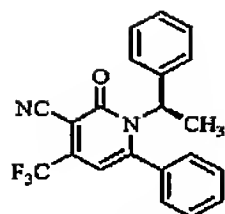


6.13

2-Oxo-1,6-diphenyl-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile

$^1\text{H-NMR}$ (CDCl_3): δ 7.35-7.27 (m, 4H), 7.26-7.20 (m, 2H), 7.13-7.03 (m, 4H), 6.56 (s, 1H). MS(ES⁺): 341.1 (M+H)

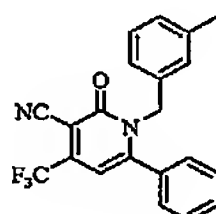
-195-



6.14

2-Oxo-6-phenyl-1-(1-phenyl-ethyl)-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile

$^1\text{H-NMR}$ (CDCl_3): δ 7.6-7.39 (m, 5H), 7.34-7.20 (m, 3H), 7.15 (d, $J=6.8\text{Hz}$, 2H), 6.37 (s, 1H), 5.60-5.49 (m, 1H), 1.95 (d, $J=6.8\text{Hz}$, 3H).

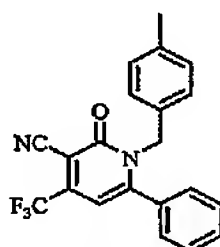


6.15

1-(3-Methyl-benzyl)-2-oxo-6-phenyl-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile

5

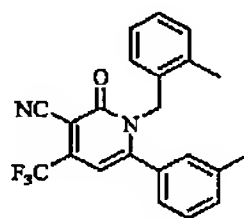
MS(ES⁺): 369.1 (M+H)



6.16

1-(4-Methyl-benzyl)-6-(1-methylene-but-2-enyl)-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile

$^1\text{H-NMR}$ (CDCl_3): δ 7.58-7.51 (m, 1H), 7.49-7.43 (m, 2H), 7.20 (d, $J=7.3\text{Hz}$, 2H), 7.03 (d, $J=8.1\text{Hz}$, 2H), 6.78 (d, $J=7.8\text{Hz}$, 2H), 6.38 (s, 1H), 5.22 (s, 2H), 2.29 (s, 3H), 1.54 (s, 3H).

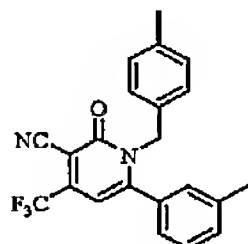


6.17

1-(2-Methyl-benzyl)-2-oxo-6-*m*-tolyl-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile

10

-196-

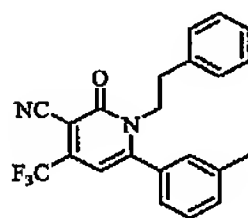
MS(ES⁺): 383.0 (M+H)

6.18

1-(4-Methyl-benzyl)-2-oxo-6-*m*-tolyl-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile

¹H-NMR (CDCl₃): δ 7.36-7.33 (m, 2H), 7.06-6.98 (m, 3H), 6.93 (bs, 1H), 6.79 (d, J=7.8Hz, 2H), 6.37 (s, 1H), 5.20 (bs, 2H), 2.34 (s, 3H), 2.30 (s, 3H).

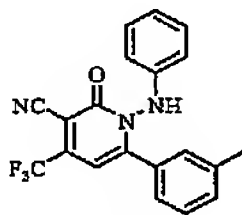
5



6.19

2-Oxo-1-phenethyl-6-*m*-tolyl-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile

¹H-NMR (CDCl₃): δ 7.40-7.33 (m, 2H), 7.23-7.18 (m, 3H), 6.97-6.93 (m, 1H), 6.89-6.83 (m, 3H), 6.31 (s, 1H), 4.23-4.16 (m, 2H), 2.97-2.90 (m, 2H), 2.40 (s, 3H).



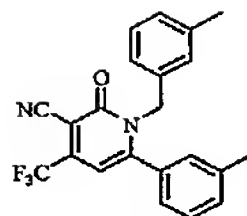
6.20

2-Oxo-1-phenylamino-6-*m*-tolyl-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile

10

¹H-NMR (CDCl₃): δ 7.91-7.84 (m, 1H), 7.47 (s, 1H), 7.38-7.32 (m, 2H), 7.18 (t, J=7.6Hz, 2H), 6.97 (t, J=7.3Hz, 1H), 6.62-6.56 (m, 3H), 2.35 (s, 3H)..

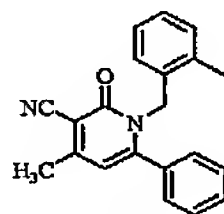
-197-



6.21

1-(3-Methyl-benzyl)-2-oxo-6-*m*-tolyl-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile

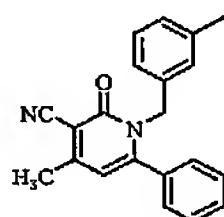
MS(ES⁺): 383.0 (M+H)



6.22

4-Methyl-1-(2-methyl-benzyl)-2-oxo-6-phenyl-1,2-dihydro-pyridine-3-carbonitrile

MS(ES⁺): 315.0 (M+H)

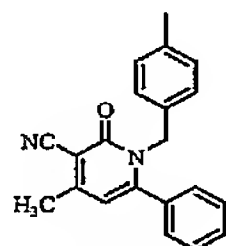


6.23

4-Methyl-1-(3-methyl-benzyl)-2-oxo-6-phenyl-1,2-dihydro-pyridine-3-carbonitrile

5

MS(ES⁺): 315.1 (M+H)

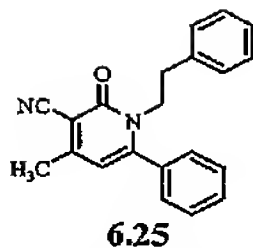


6.24

4-Methyl-1-(4-methyl-benzyl)-2-oxo-6-phenyl-1,2-dihydro-pyridine-3-carbonitrile

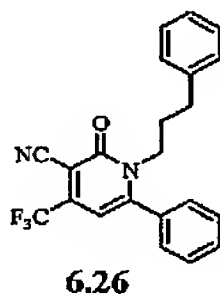
MS(ES⁺): 315.0 (M+H)

-198-



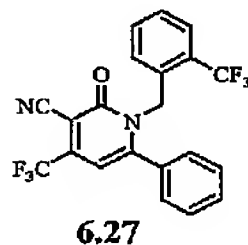
4-Methyl-2-oxo-1-phenethyl-6-phenyl-1,2-dihydro-pyridine-3-carbonitrile

MS(ES⁺): 315.2 (M+H)



2-Oxo-6-phenyl-1-(3-phenyl-propyl)-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile

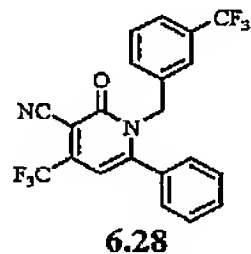
MS(ES⁺): 383.3 (M+H)



2-Oxo-6-phenyl-4-trifluoromethyl-1-(2-trifluoromethyl-benzyl)-1,2-dihydro-pyridine-3-carbonitrile

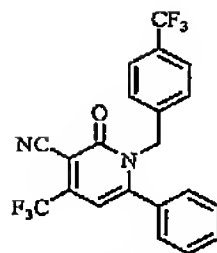
5

¹H-NMR (CDCl₃): δ 7.64-7.32 (m, 6H), 7.07 (d, J=6.8Hz, 2H), 6.93 (d, J=7.8Hz, 1H), 6.50 (s, 1H), 5.37 (s, 2H).



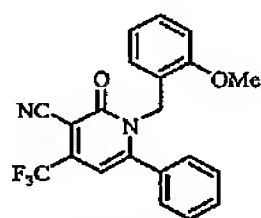
2-Oxo-6-phenyl-4-trifluoromethyl-1-(3-trifluoromethyl-benzyl)-1,2-dihydro-pyridine-3-carbonitrile

MS(ES⁺): 422.8 (M+H)

-199-**6.29**

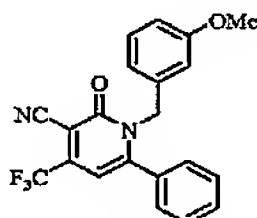
2-Oxo-6-phenyl-4-trifluoromethyl-1-(4-trifluoromethyl-benzyl)-
1,2-dihydro-pyridine-3-carbonitrile

MS(ES⁺): 422.8 (M+H)

**6.30**

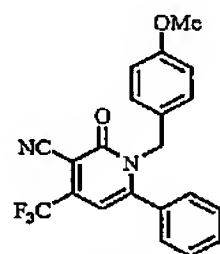
1-(2-Methoxy-benzyl)-2-oxo-6-phenyl-4-trifluoromethyl-
1,2-dihydro-pyridine-3-carbonitrile

MS(ES⁺): 383.3 (M+H)

**6.31**

1-(3-Methoxy-benzyl)-2-oxo-6-phenyl-4-trifluoromethyl-
1,2-dihydro-pyridine-3-carbonitrile

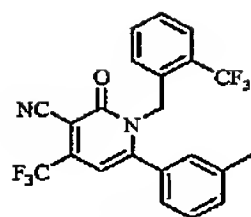
MS(ES⁺): 384.9 (M+H)

**6.32**

1-(4-Methoxy-benzyl)-2-oxo-6-phenyl-4-trifluoromethyl-
1,2-dihydro-pyridine-3-carbonitrile

MS(ES⁺): 385.3 (M+H)

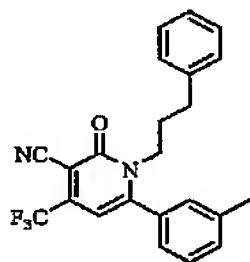
-200-



6.33

2-Oxo-6-*m*-tolyl-4-trifluoromethyl-1-(2-trifluoromethyl-benzyl)-
1,2-dihydro-pyridine-3-carbonitrile

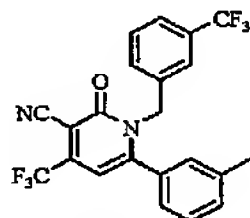
MS(ES⁺): 459.2 (M+Na)



6.34

2-Oxo-1-(3-phenyl-propyl)-6-*m*-tolyl-4-trifluoromethyl-1,2-
dihydro-pyridine-3-carbonitrile

MS(ES⁺): 397.0 (M+H)

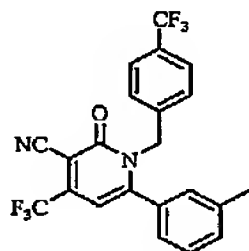


6.35

2-Oxo-6-*m*-tolyl-4-trifluoromethyl-1-(3-trifluoromethyl-benzyl)-
1,2-dihydro-pyridine-3-carbonitrile

5

MS(ES⁺): 438.0 (M+H)

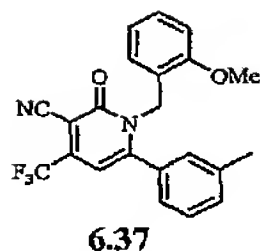


6.36

2-Oxo-6-*m*-tolyl-4-trifluoromethyl-1-(4-trifluoromethyl-benzyl)-
1,2-dihydro-pyridine-3-carbonitrile

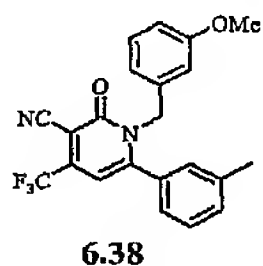
MS(ES⁺): 437.0 (M+H)

-201-



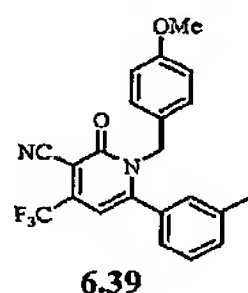
1-(2-Methoxy-benzyl)-2-oxo-6-*m*-tolyl-4-trifluoromethyl-
1,2-dihydro-pyridine-3-carbonitrile

MS(ES⁺): 420.8 (M+Na)



1-(3-Methoxy-benzyl)-2-oxo-6-*m*-tolyl-4-trifluoromethyl-
1,2-dihydro-pyridine-3-carbonitrile

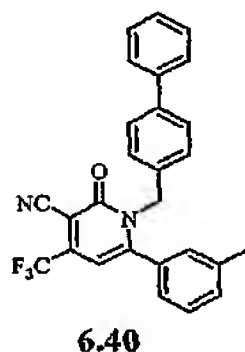
MS(ES⁺): 398.8 (M+H)



1-(4-Methoxy-benzyl)-2-oxo-6-*m*-tolyl-4-trifluoromethyl-
1,2-dihydro-pyridine-3-carbonitrile

5

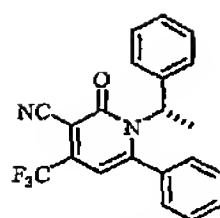
MS(ES⁺): 421.0 (M+Na)



1-Biphenyl-4-ylmethyl-2-oxo-6-*m*-tolyl-4-trifluoromethyl-
1,2-dihydro-pyridine-3-carbonitrile

MS(ES⁺): 467.0 (M+Na)

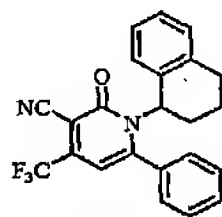
-202-



6.41

2-Oxo-6-phenyl-1-(1-phenyl-ethyl)-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile

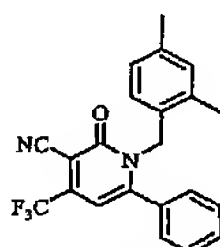
MS(ES⁺): 369.3 (M+H)



6.42

2-Oxo-6-phenyl-1-(1,2,3,4-tetrahydronaphthalen-1-yl)-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile

MS(ES⁺): 395.0 (M+H)

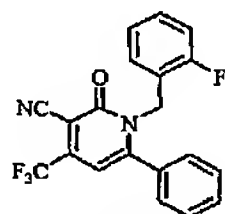


6.43

1-(2,4-Dimethyl-benzyl)-2-oxo-6-phenyl-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile

5

MS(ES⁺): 405.2 (M+Na)

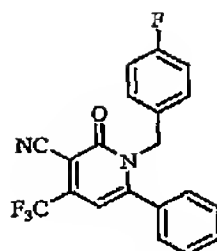


6.44

1-(2-Fluoro-benzyl)-2-oxo-6-phenyl-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile

MS(ES⁺): 373.0 (M+H)

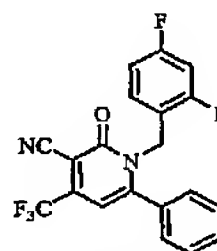
-203-



6.45

1-(4-Fluoro-benzyl)-2-oxo-6-phenyl-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile

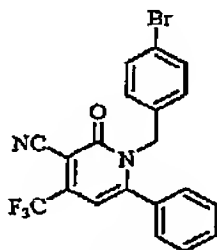
MS(ES⁺): 373.0 (M+H)



6.46

1-(2,4-Difluoro-benzyl)-2-oxo-6-phenyl-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile

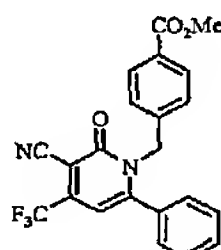
MS(ES⁺): 390.8 (M+H)



6.47

1-(4-Bromo-benzyl)-2-oxo-6-phenyl-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile

MS(ES⁺): 435.0 (M+H)

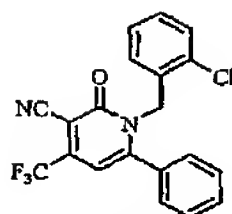


6.48

4-(3-Cyano-2-oxo-6-phenyl-4-trifluoromethyl-2H-pyridin-1-ylmethyl)-benzoic acid methyl ester

MS(ES⁺): 413.2 (M+H)

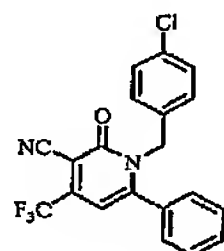
-204-



6.49

1-(2-Chloro-benzyl)-2-oxo-6-phenyl-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile

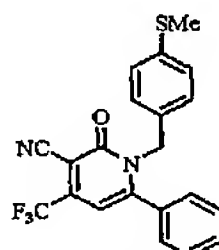
MS(ES⁺): 389.0 (M+H)



6.50

1-(4-Chloro-benzyl)-2-oxo-6-phenyl-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile

MS(ES⁺): 389.0 (M+H)

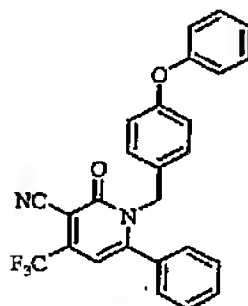


6.51

1-(4-Methylsulfanyl-benzyl)-2-oxo-6-phenyl-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile

5

MS(ES⁺): 423.0 (M+Na)

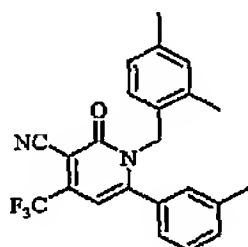


6.52

2-Oxo-1-(4-phenoxy-benzyl)-6-phenyl-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile

-205-

$^1\text{H-NMR}$ (CDCl_3): δ 7.59-7.53 (m, 1H), 7.48 (t, $J=7.8\text{Hz}$, 2H), 7.37-7.30 (m, 2H), 7.25-7.20 (m, 2H), 7.15-7.09 (m, 1H), 7.00-6.95 (m, 2H), 6.88-6.81 (m, 4H), 6.39 (s, 1H), 5.24 (s, 2H).

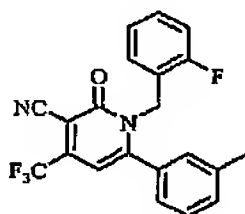


6.53

1-(2,4-Dimethyl-benzyl)-2-oxo-6-*m*-tolyl-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile

5

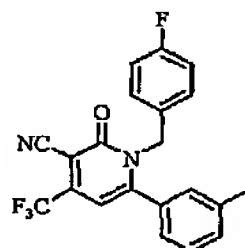
MS(ES⁺): 397.0 (M+H)



6.54

1-(2-Fluoro-benzyl)-2-oxo-6-*m*-tolyl-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile

MS(ES⁺): 387.0 (M+H)

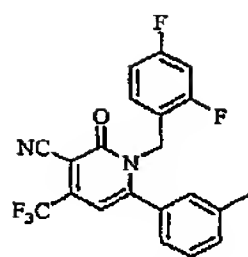


6.55

1-(4-Fluoro-benzyl)-2-oxo-6-*m*-tolyl-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile

MS(ES⁺): 387.0 (M+H)

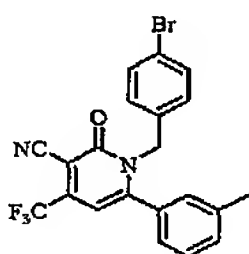
-206-



6.56

1-(2,4-Difluoro-benzyl)-2-oxo-6-*m*-tolyl-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile

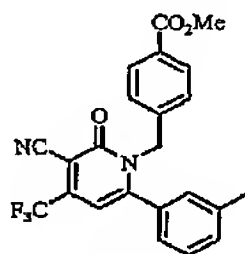
MS(ES⁺): 405.0 (M+H)



6.57

1-(4-Bromo-benzyl)-2-oxo-6-*m*-tolyl-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile

MS(ES⁺): 449.0 (M+H)

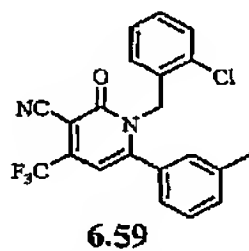


6.58

4-(3-Cyano-2-oxo-6-*m*-tolyl-4-trifluoromethyl-2*H*-pyridin-1-ylmethyl)-benzoic acid methyl ester

5

MS(ES⁺): 427.2 (M+H)

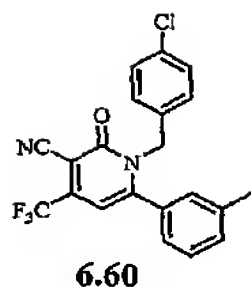


6.59

1-(2-Chloro-benzyl)-2-oxo-6-*m*-tolyl-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile

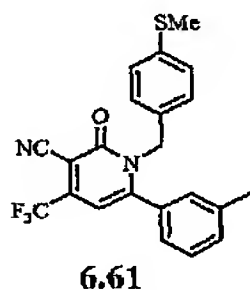
MS(ES⁺): 403.0 (M+H)

-207-



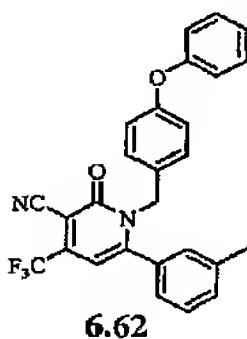
1-(4-Chloro-benzyl)-2-oxo-6-*m*-tolyl-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile

MS(ES⁺): 402.8 (M+H)



1-(4-Methylsulfanyl-benzyl)-2-oxo-6-*m*-tolyl-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile

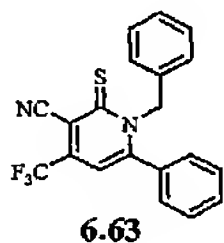
MS(ES⁺): 437.2 (M+Na)



2-Oxo-1-(4-phenoxy-benzyl)-6-*m*-tolyl-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile

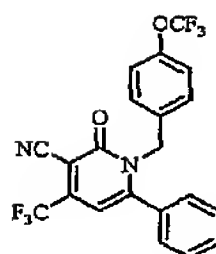
5

¹H-NMR (CDCl₃): δ 7.40-7.30 (m, 4H), 7.14-7.09 (m, 1H), 7.05-6.94 (m, 4H), 6.90-6.83 (m, 4H), 6.39 (s, 1H), 5.22 (s, 2H), 2.36 (s, 3H).



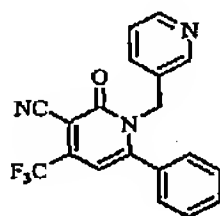
1-Benzyl-6-phenyl-2-thioxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile

MS(ES⁺): 370.9 (M+H)

-208-**6.64**

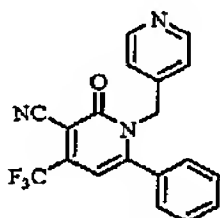
2-Oxo-6-phenyl-1-(4-trifluoromethoxy-benzyl)-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile

MS(ES⁺): 439.2 (M+H)

**6.65**

2-Oxo-6-phenyl-1-pyridin-3-ylmethyl-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile

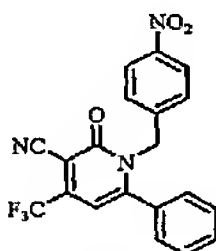
MS(ES⁺): 355.8 (M+H)

**6.66**

2-Oxo-6-phenyl-1-pyridin-4-ylmethyl-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile

5

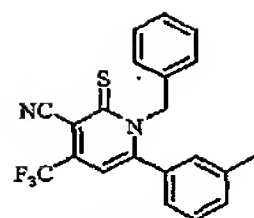
MS(ES⁺): 355.8 (M+H)

**6.67**

1-(4-Nitro-benzyl)-2-oxo-6-phenyl-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile

MS(ES⁺): 400.0 (M+H)

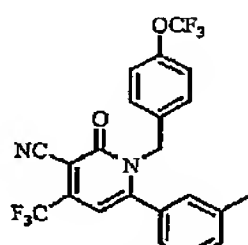
-209-



6.68

1-Benzyl-2-thioxo-6-*m*-tolyl-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile

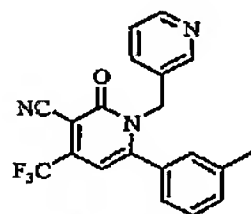
MS(ES⁺): 385.3 (M+H)



6.69

2-Oxo-6-*m*-tolyl-1-(4-trifluoromethoxy-benzyl)-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile

MS(ES⁺): 453.0 (M+H)

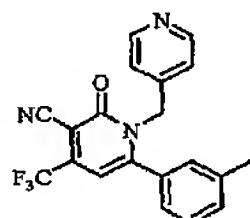


6.70

2-Oxo-1-pyridin-3-ylmethyl-6-*m*-tolyl-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile

5

MS(ES⁺): 369.8 (M+H)

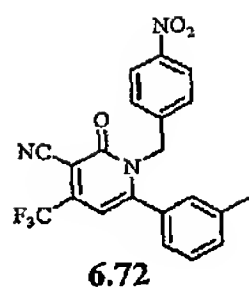


6.71

2-Oxo-1-pyridin-4-ylmethyl-6-*m*-tolyl-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile

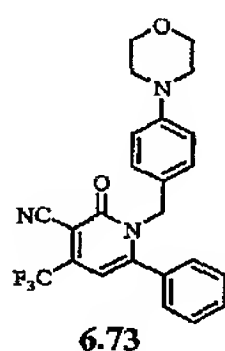
MS(ES⁺): 369.8 (M+H)

-210-



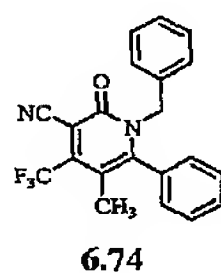
1-(4-Nitro-benzyl)-2-oxo-6-*m*-tolyl-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile

MS(ES⁺): 414.0 (M+H)



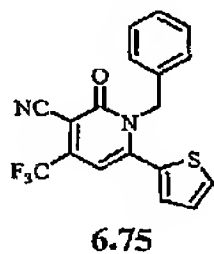
1-(4-Morpholin-4-yl-benzyl)-2-oxo-6-phenyl-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile

MS(ES⁺): 440.2 (M+H)



1-Benzyl-5-methyl-2-oxo-6-phenyl-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile

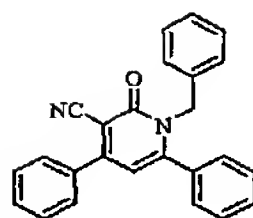
MS(ES⁺): 369.0(M+H)



1-Benzyl-2-oxo-6-thiophen-2-yl-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile

MS(ES⁺): 383.0 (M+Na)

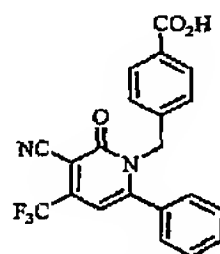
-211-



6.76

1-Benzyl-2-oxo-4,6-diphenyl-1,2-dihydro-
pyridine-3-carbonitrile

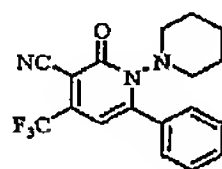
MS(ES⁺): 385.2 (M+Na)



6.77

4-(3-Cyano-2-oxo-6-phenyl-4-trifluoromethyl-2H-
pyridin-1-ylmethyl)-benzoic acid

MS(ES⁺): 399.4 (M+H)

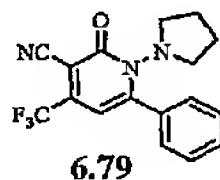


6.78

2-Oxo-6-phenyl-4-trifluoromethyl-3',4',5',6'-tetrahydro-
2H,2'H-[1,1']bipyridinyl-3-carbonitrile

5

MS(ES⁺): 348.0 (M+H)

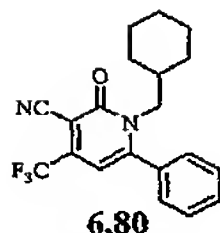


6.79

2-Oxo-6-phenyl-1-pyrrolidin-1-yl-4-trifluoromethyl-1,2-
dihydro-pyridine-3-carbonitrile

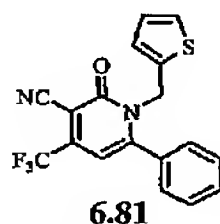
MS(ES⁺): 334.0 (M+H)

-212-



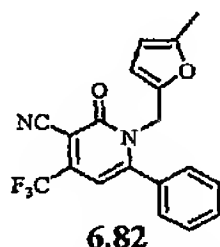
1-Cyclohexylmethyl-2-oxo-6-phenyl-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile

MS(ES⁺): 361.0 (M+H)



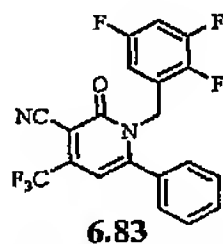
2-Oxo-6-phenyl-1-(thiophen-2-ylmethyl)-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile

MS(ES⁺): 361.1 (M+H)



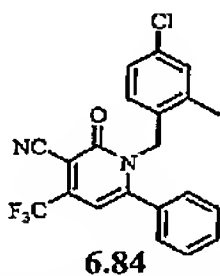
1-(5-Methyl-furan-2-ylmethyl)-2-oxo-6-phenyl-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile

MS(ES⁺): 381.0 (M+Na)



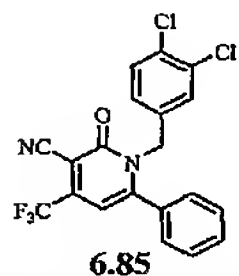
2-Oxo-6-phenyl-1-(2,3,5-trifluorobenzyl)-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile

MS(ES⁺): 409.2 (M+H)

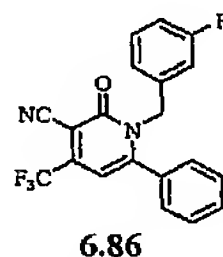


1-(4-Chloro-2-methylbenzyl)-2-oxo-6-phenyl-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile

-213-

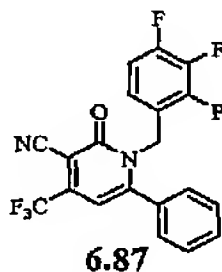
MS(ES⁺): 403.0 (M+H)

1-(3,4-Dichloro-benzyl)-2-oxo-6-phenyl-4-trifluoromethyl-
1,2-dihydro-pyridine-3-carbonitrile

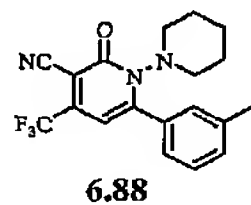
MS(ES⁺): 423.0 (M+H)

1-(3-Fluoro-benzyl)-2-oxo-6-phenyl-4-trifluoromethyl-1,2-
dihydro-pyridine-3-carbonitrile

5

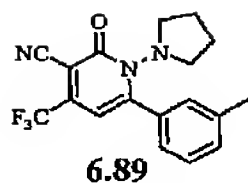
MS(ES⁺): 373.0 (M+H)

2-Oxo-6-phenyl-1-(2,3,4-trifluoro-benzyl)-4-trifluoromethyl-
1,2-dihydro-pyridine-3-carbonitrile

MS(ES⁺): 409.2 (M+H)

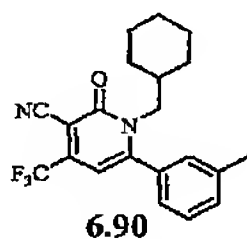
2-Oxo-6-*m*-tolyl-4-trifluoromethyl-
3',4',5',6'-tetrahydro-2*H*,2'*H*-
[1,1']bipyridinyl-3-carbonitrile

MS(ES⁺): 362.0 (M+H)

-214-

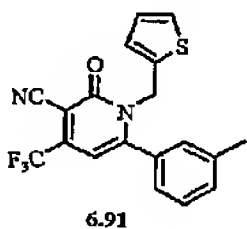
2-Oxo-1-pyrrolidin-1-yl-6-*m*-tolyl-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile

MS(ES⁺): 348.0 (M+H)



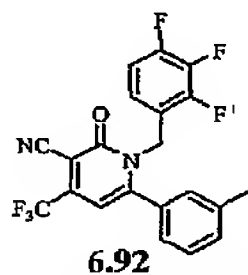
1-Cyclohexylmethyl-2-oxo-6-*m*-tolyl-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile

MS(ES⁺): 375.0 (M+H)

5

2-Oxo-1-thiophen-2-ylmethyl-6-*m*-tolyl-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile

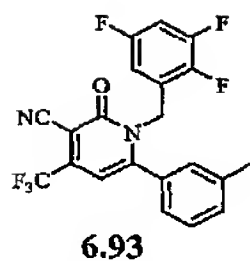
MS(ES⁺): 375.0 (M+H)



2-Oxo-6-*m*-tolyl-1-(2,3,4-trifluoro-benzyl)-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile

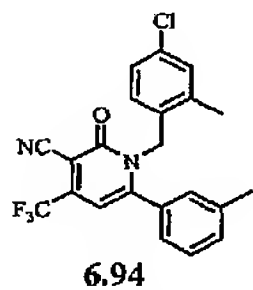
MS(ES⁺): 423.0 (M+H)

-215-



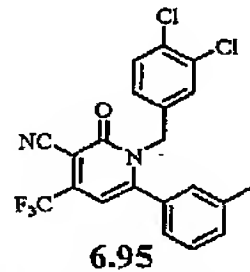
2-Oxo-6-*m*-tolyl-1-(2,3,5-trifluoro-benzyl)-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile

MS(ES⁺): 423.0 (M+H)



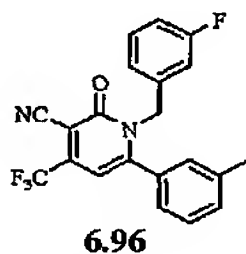
1-(4-Chloro-2-methyl-benzyl)-2-oxo-6-*m*-tolyl-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile

MS(ES⁺): 417.0 (M+H)



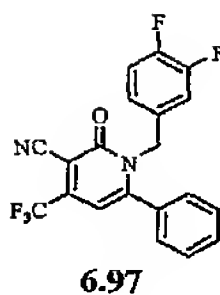
1-(3,4-Dichloro-benzyl)-2-oxo-6-*m*-tolyl-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile

MS(ES⁺): 437.0 (M+H)



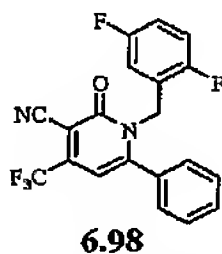
1-(3-Fluoro-benzyl)-2-oxo-6-*m*-tolyl-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile

MS(ES⁺): 387.0 (M+H)

-216-

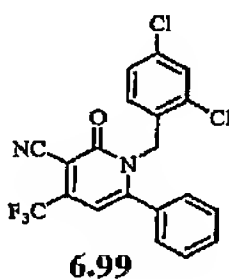
1-(3,4-Difluoro-benzyl)-2-oxo-6-phenyl-4-trifluoromethyl-
1,2-dihydro-pyridine-3-carbonitrile

MS(ES⁺): 390.8 (M+H)



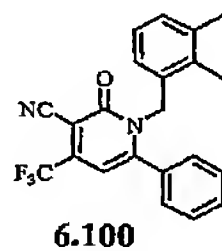
1-(2,5-Difluoro-benzyl)-2-oxo-6-phenyl-4-trifluoromethyl-
1,2-dihydro-pyridine-3-carbonitrile

MS(ES⁺): 390.8 (M+H)



1-(2,4-Dichloro-benzyl)-2-oxo-6-phenyl-4-trifluoromethyl-
1,2-dihydro-pyridine-3-carbonitrile

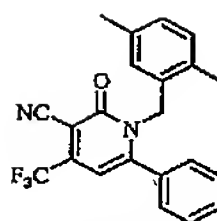
MS(ES⁺): 423.0 (M+H)



1-(2,3-Dimethyl-benzyl)-2-oxo-6-phenyl-4-trifluoromethyl-
1,2-dihydro-pyridine-3-carbonitrile

MS(ES⁺): 383.2 (M+H)

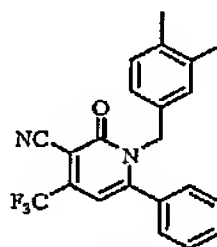
-217-



6.101

1-(2,5-Dimethyl-benzyl)-2-oxo-6-phenyl-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile

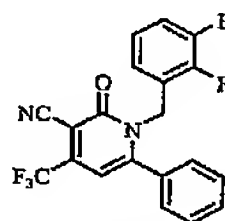
MS(ES⁺): 383.0 (M+H)



6.102

1-(3,4-Dimethyl-benzyl)-2-oxo-6-phenyl-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile

MS(ES⁺): 383.2 (M+H)

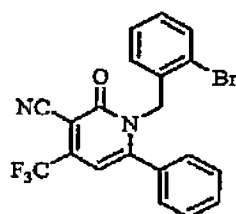


6.103

1-(2,3-Difluoro-benzyl)-2-oxo-6-phenyl-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile

5

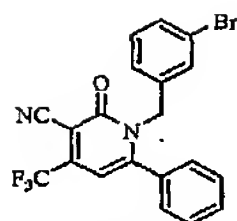
MS(ES⁺): 391.0 (M+H)



6.104

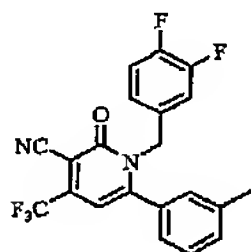
1-(2-Bromo-benzyl)-2-oxo-6-phenyl-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile

MS(ES⁺): 433.0 (M+H)

-218-**6.105**

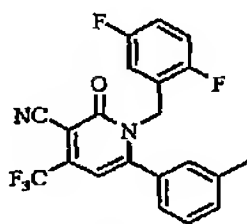
1-(3-Bromo-benzyl)-2-oxo-6-phenyl-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile

MS(ES⁺): 435.0 (M+H)

**6.106**

1-(3,4-Difluoro-benzyl)-2-oxo-6-*m*-tolyl-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile

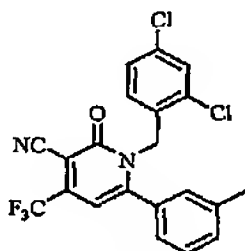
MS(ES⁺): 405.0 (M+H)

**6.107**

1-(2,5-Difluoro-benzyl)-2-oxo-6-*m*-tolyl-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile

5

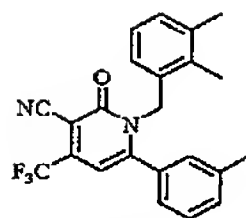
MS(ES⁺): 405.0 (M+H)

**6.108**

1-(2,4-Dichloro-benzyl)-2-oxo-6-*m*-tolyl-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile

MS(ES⁺): 437.2 (M+H)

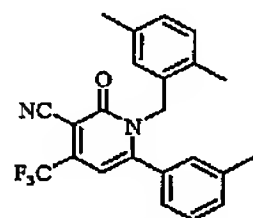
-219-



6.109

1-(2,3-Dimethyl-benzyl)-2-oxo-6-*m*-tolyl-4-trifluoromethyl-
1,2-dihydro-pyridine-3-carbonitrile

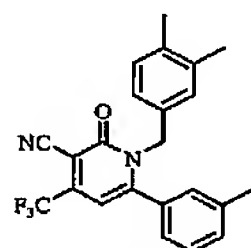
MS(ES⁺): 397.0 (M+H)



6.110

1-(2,5-Dimethyl-benzyl)-2-oxo-6-
m-tolyl-4-trifluoromethyl-1,2-
dihydro-pyridine-3-carbonitrile

MS(ES⁺): 397.0 (M+H)

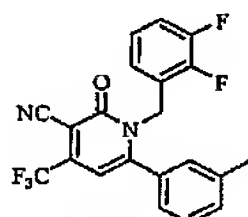


6.111

1-(3,4-Dimethyl-benzyl)-2-oxo-6-
m-tolyl-4-trifluoromethyl-1,2-
dihydro-pyridine-3-carbonitrile

5

MS(ES⁺): 397.0 (M+H)

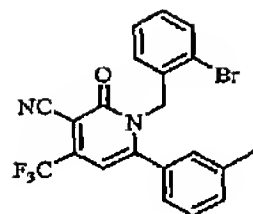


6.112

1-(2,3-Difluoro-benzyl)-2-oxo-6-
m-tolyl-4-trifluoromethyl-1,2-
dihydro-pyridine-3-carbonitrile

MS(ES⁺): 405.0 (M+H)

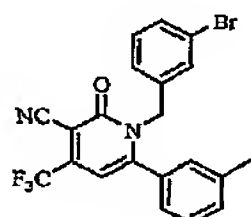
-220-



6.113

1-(2-Bromo-benzyl)-2-oxo-6-*m*-tolyl-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile

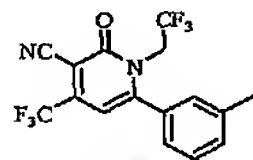
MS(ES⁺): 449.1(M+H)



6.114

1-(3-Bromo-benzyl)-2-oxo-6-*m*-tolyl-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile

MS(ES⁺): 447.0 (M+H)

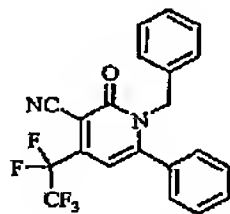


6.115

2-Oxo-6-*m*-tolyl-1-(2,2,2-trifluoroethyl)-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile

5

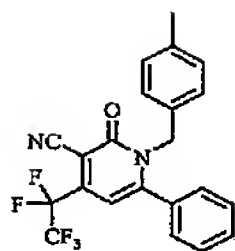
MS(ES⁺): 347.0 (M+H)



6.116

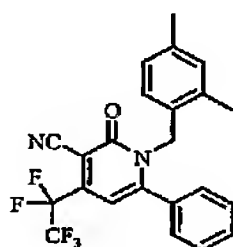
1-Benzyl-2-oxo-4-pentafluoroethyl-6-phenyl-1,2-dihydro-pyridine-3-carbonitrile

¹H-NMR (CDCl₃): δ 7.58-7.52 (m, 1H), 7.45 (t, J=7.8Hz, 2H), 7.26-7.16 (m, 5H), 6.92-6.86 (m, 2H), 6.32 (s, 1H), 5.26 (s, 2H).

-221-**6.117**

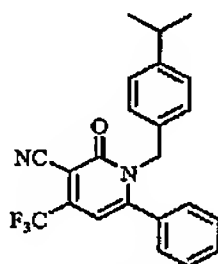
1-(4-Methyl-benzyl)-2-oxo-4-pentafluoroethyl-6-phenyl-
1,2-dihydro-pyridine-3-carbonitrile

MS(ES⁺): 419.3 (M+H)

**6.118**

1-(2,4-Dimethyl-benzyl)-2-oxo-4-pentafluoroethyl-6-phenyl-
1,2-dihydro-pyridine-3-carbonitrile

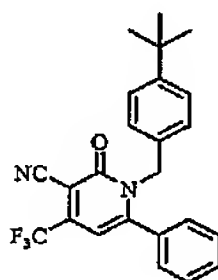
MS(ES⁺): 433.3 (M+H)

**6.119**

1-(4-Isopropyl-benzyl)-2-oxo-6-phenyl-4-trifluoromethyl-
1,2-dihydro-pyridine-3-carbonitrile

5

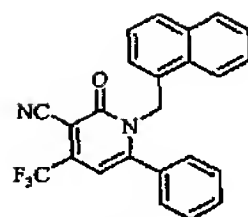
MS(ES⁺): 397.1 (M+H)

**6.120**

1-(4-*tert*-Butyl-benzyl)-2-oxo-6-phenyl-4-trifluoromethyl-
1,2-dihydro-pyridine-3-carbonitrile

MS(ES⁺): 411.4 (M+H)

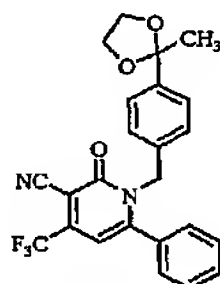
-222-



6.121

1-Naphthalen-1-ylmethyl-2-oxo-6-phenyl-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile

$^1\text{H-NMR}$ (CDCl_3): δ 7.86 (d, $J=7.8\text{Hz}$, 1H), 7.79 (d, $J=8.3\text{Hz}$, 1H), 7.58 (d, $J=8.6\text{Hz}$, 1H), 7.52-7.35 (m, 4H), 7.16-7.14 (m, 2H), 6.87 (d, $J=7.3\text{Hz}$, 1H), 6.49 (s, 1H), 5.68 (s, 2H).

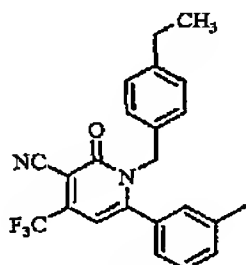


6.122

1-[4-(2-Methyl-[1,3]dioxolan-2-yl)-benzyl]-2-oxo-6-phenyl-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile

5

$^1\text{H-NMR}$ (CDCl_3): δ 7.59-7.52 (m, 1H), 7.46 (t, $J=8.1\text{Hz}$, 2H), 7.34 (d, $J=8.1\text{Hz}$, 2H), 7.23 (d, $J=7.1\text{Hz}$, 2H), 6.88 (d, $J=8.1\text{Hz}$, 2H), 6.41 (s, 1H), 5.25 (s, 2H), 4.05-3.99 (m, 2H), 3.75-3.70 (m, 2H), 1.60 (s, 3H).



6.123

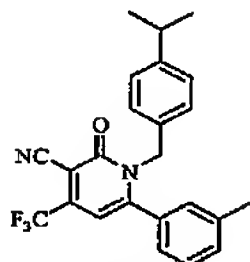
1-(4-Ethyl-benzyl)-2-oxo-6-m-tolyl-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile

10

$^1\text{H-NMR}$ (CDCl_3): δ 7.36-7.31 (m, 2H), 7.06 (d, $J=8.1\text{Hz}$, 2H), 7.04-6.99 (m, 1H), 6.91 (bs, 1H), 6.81 (d, $J=8.1\text{Hz}$, 2H), 6.37 (s, 1H),

-223-

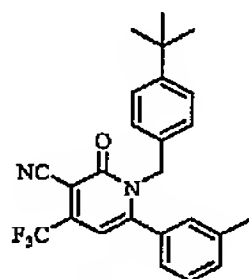
5.21 (bs, 2H), 2.59 (q, J=7.6Hz, 2H), 2.33 (s, 3H), 1.19 (t, J=7.3Hz, 3H).



6.124

1-(4-Isopropyl-benzyl)-2-oxo-6-*m*-tolyl-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile

MS(ES⁺): 411.4 (M+H)

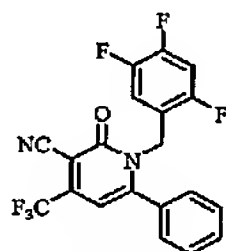


6.125

1-(4-*tert*-Butyl-benzyl)-2-oxo-6-*m*-tolyl-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile

5

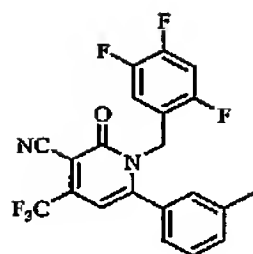
MS(ES⁺): 424.9 (M+H)



6.126

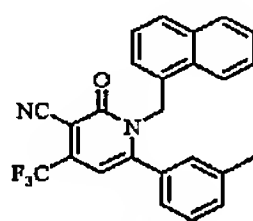
2-Oxo-6-phenyl-1-(2,4,5-trifluoro-benzyl)-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile

MS(ES⁺): 409.2 (M+H)

-224-**6.127**

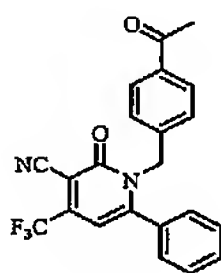
2-Oxo-6-*m*-tolyl-1-(2,4,5-trifluoro-benzyl)-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile

MS(ES⁺): 423.1 (M+H)

**6.128**

1-Naphthalen-1-ylmethyl-2-oxo-6-*m*-tolyl-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile

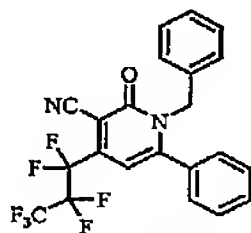
MS(ES⁺): 419.2 (M+H)

**6.129**

1-(4-Acetyl-benzyl)-2-oxo-6-phenyl-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile

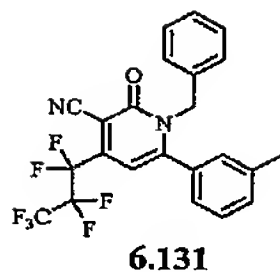
5

MS(ES⁺): 397.2 (M+H)

**6.130**

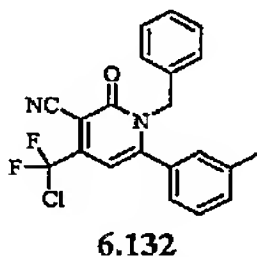
1-Benzyl-4-heptafluoropropyl-2-oxo-6-phenyl-1,2-dihydro-pyridine-3-carbonitrile

MS(ES⁺): 455.2 (M+H)

-225-

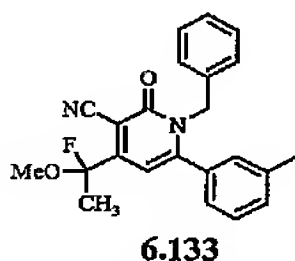
1-Benzyl-4-heptafluoropropyl-2-oxo-6-*m*-tolyl-1,2-dihydro-pyridine-3-carbonitrile

MS(ES⁺): 469.0 (M+H)



1-Benzyl-4-(chloro-difluoro-methyl)-2-oxo-6-*m*-tolyl-1,2-dihydro-pyridine-3-carbonitrile

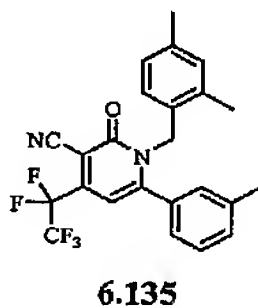
MS(ES⁺): 385.2 (M+H)



1-Benzyl-4-(1-fluoro-1-methoxy-ethyl)-2-oxo-6-*m*-tolyl-1,2-dihydro-pyridine-3-carbonitrile

5

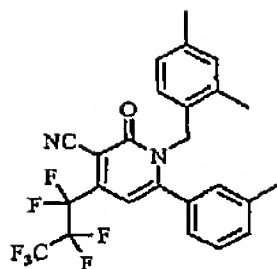
¹H-NMR (CDCl₃): δ 7.34-7.31 (m, 2H), 7.26-7.22 (m, 2H), 7.02-6.88 (m, 4H), 6.35 (s, 1H), 5.23 (s, 2H), 3.66 (s, 3H), 2.32 (s, 3H).



1-(2,4-Dimethyl-benzyl)-2-oxo-4-pentafluoroethyl-6-*m*-tolyl-1,2-dihydro-pyridine-3-carbonitrile

MS(ES⁺): 447.3 (M+H)

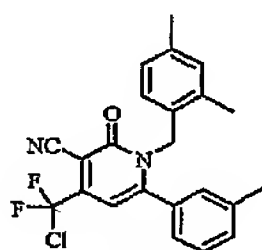
-226-



6.136

1-(2,4-Dimethyl-benzyl)-4-heptafluoropropyl-2-oxo-6-*m*-tolyl-
1,2-dihydro-pyridine-3-carbonitrile

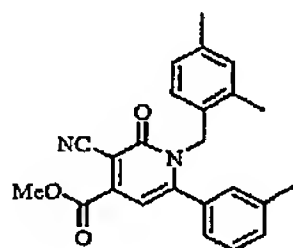
MS(ES⁺): 497.2 (M+H)



6.137

4-(Chloro-difluoro-methyl)-1-(2,4-
dimethyl-benzyl)-2-oxo-6-*m*-tolyl-1,2-
dihydro-pyridine-3-carbonitrile

MS(ES⁺): 413.1 (M+H)

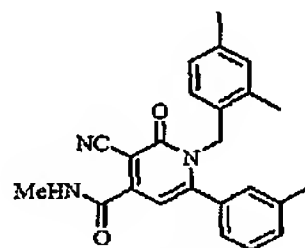


6.138

3-Cyano-1-(2,4-dimethyl-benzyl)-2-
oxo-6-*m*-tolyl-1,2-dihydro-pyridine-
4-carboxylic acid methyl ester

5

MS(ES⁺): 387.1 (M+H)

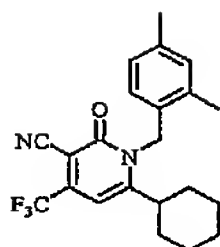


6.139

3-Cyano-1-(2,4-dimethyl-benzyl)-2-oxo-6-*m*-tolyl-1,2-
dihydro-pyridine-4-carboxylic acid methylamide

MS(ES⁺): 386.1 (M+H)

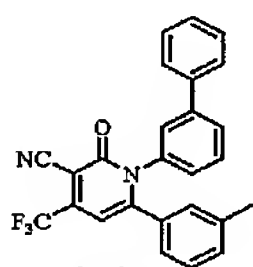
-227-



6.140

6-Cyclohexyl-1-(2,4-dimethylbenzyl)-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile

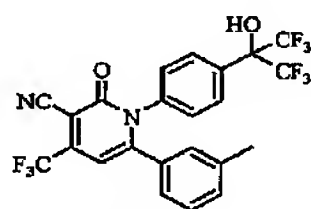
MS(ES⁺): 389.3 (M+H)



6.141

1-Biphenyl-3-yl-2-oxo-6-*m*-tolyl-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile

MS(ES⁺): 431.0 (M+H)

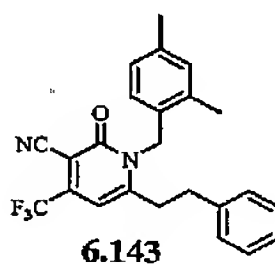


6.142

2-Oxo-6-*m*-tolyl-1-[4-(2,2,2-trifluoro-1-hydroxy-1-trifluoromethyl-ethyl)-phenyl]-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile

5

MS(ES⁺): 521.2 (M+H)

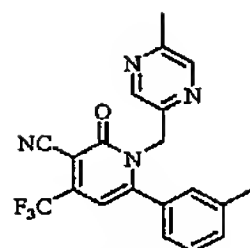


6.143

1-(2,4-Dimethyl-benzyl)-2-oxo-6-phenethyl-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile

MS(ES⁺): 411.4 (M+H)

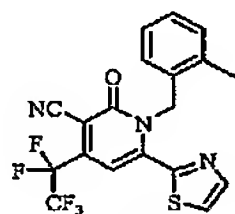
-228-



6.144

1-(5-Methyl-pyrazin-2-ylmethyl)-2-oxo-
6-*m*-tolyl-4-trifluoromethyl-1,2-dihydro-
pyridine-3-carbonitrile

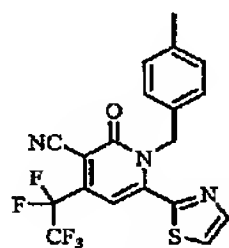
MS(ES⁺): 385.1 (M+H)



6.145

1-(2-Methyl-benzyl)-2-oxo-4-
pentafluoroethyl-6-thiazol-2-yl-1,2-
dihydro-pyridine-3-carbonitrile

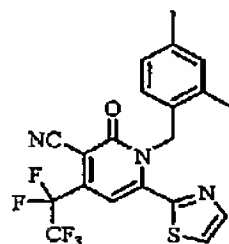
MS(ES⁺): 426.0 (M+H)



6.145

1-(4-Methyl-benzyl)-2-oxo-4-
pentafluoroethyl-6-thiazol-2-yl-1,2-
dihydro-pyridine-3-carbonitrile

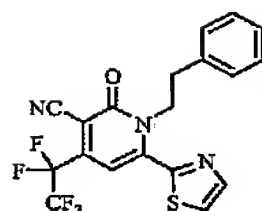
MS(ES⁺): 426.1 (M+H)



6.146

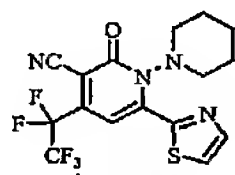
1-(2,4-Dimethyl-benzyl)-2-oxo-4-
pentafluoroethyl-6-thiazol-2-yl-1,2-
dihydro-pyridine-3-carbonitrile

MS(ES⁺): 440.2 (M+H)

-229-**6.147**

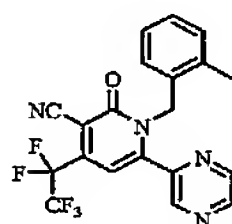
2-Oxo-4-pentafluoroethyl-1-phenethyl-6-thiazol-2-yl-1,2-dihydro-pyridine-3-carbonitrile

MS(ES⁺): 426.0 (M+H)

**6.148**

2-Oxo-4-pentafluoroethyl-6-thiazol-2-yl-3',4',5',6'-tetrahydro-2H,2'H-[1,1']bipyridinyl-3-carbonitrile

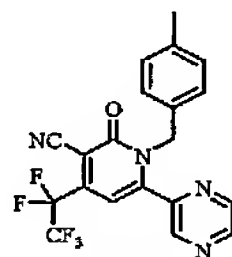
MS(ES⁺): 404.9 (M+H)

**6.149**

1-(2-Methyl-benzyl)-2-oxo-4-pentafluoroethyl-6-pyrazin-2-yl-1,2-dihydro-pyridine-3-carbonitrile

5

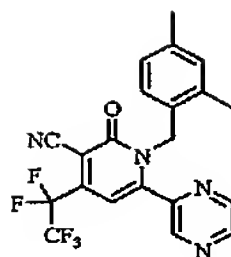
MS(ES⁺): 421.1 (M+H)

**6.150**

1-(4-Methyl-benzyl)-2-oxo-4-pentafluoroethyl-6-pyrazin-2-yl-1,2-dihydro-pyridine-3-carbonitrile

MS(ES⁺): 421.0 (M+H)

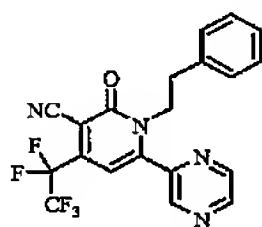
-230-



6.151

1-(2,4-Dimethyl-benzyl)-2-oxo-4-pentafluoroethyl-6-pyrazin-2-yl-1,2-dihydro-pyridine-3-carbonitrile

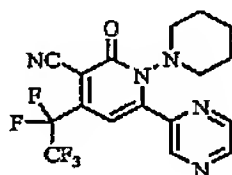
MS(ES⁺): 435.3 (M+H)



6.152

2-Oxo-4-pentafluoroethyl-1-phenethyl-6-pyrazin-2-yl-1,2-dihydro-pyridine-3-carbonitrile

MS(ES⁺): 421.1 (M+H)

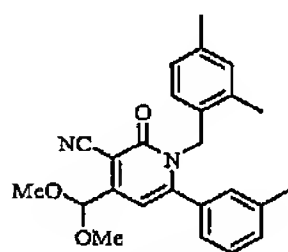


6.153

2-Oxo-4-pentafluoroethyl-6-pyrazin-2-yl-3',4',5',6'-tetrahydro-2H,2'H-[1,1']bipyridinyl-3-carbonitrile

5

MS(ES⁺): 400.3 (M+H)

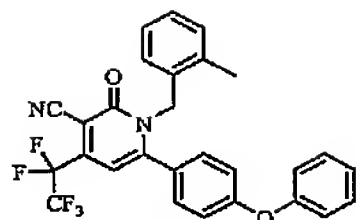


6.154

4-Dimethoxymethyl-1-(2,4-dimethyl-benzyl)-2-oxo-6-*m*-tolyl-1,2-dihydro-pyridine-3-carbonitrile

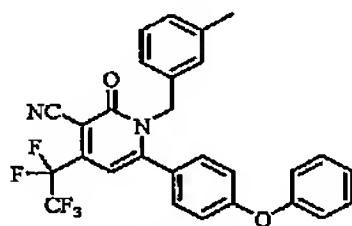
MS(ES⁺): 402.9 (M+H)

-231-



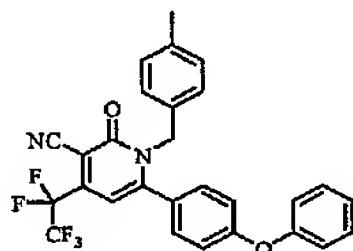
6.155

1-(2-Methyl-benzyl)-2-oxo-4-pentafluoroethyl-6-(4-phenoxy-phenyl)-1,2-dihydro-pyridine-3-carbonitrile

MS(ES⁺): 511.1 (M+H)

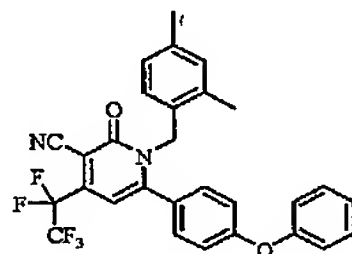
6.156

1-(3-Methyl-benzyl)-2-oxo-4-pentafluoroethyl-6-(4-phenoxy-phenyl)-1,2-dihydro-pyridine-3-carbonitrile

MS(ES⁺): 511.3 (M+H)

6.157

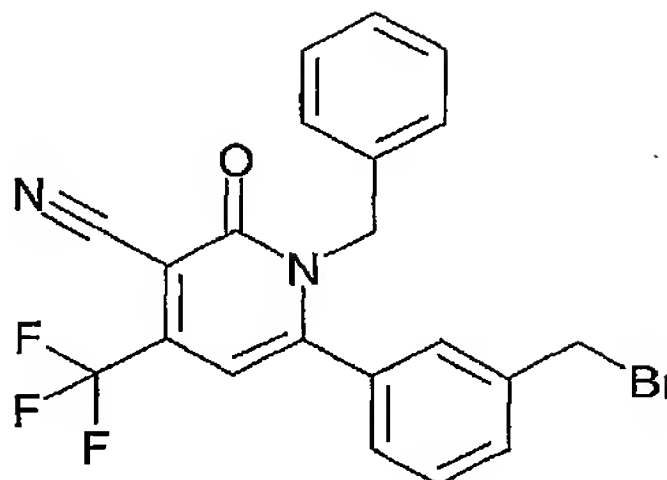
1-(4-Methyl-benzyl)-2-oxo-4-pentafluoroethyl-6-(4-phenoxy-phenyl)-1,2-dihydro-pyridine-3-carbonitrile

MS(ES⁺): 510.9 (M+H)

6.158

1-(2,4-Dimethyl-benzyl)-2-oxo-4-pentafluoroethyl-6-(4-phenoxy-phenyl)-1,2-dihydro-pyridine-3-carbonitrile

-232-

MS(ES⁺): 525.4 (M+H)

6.159

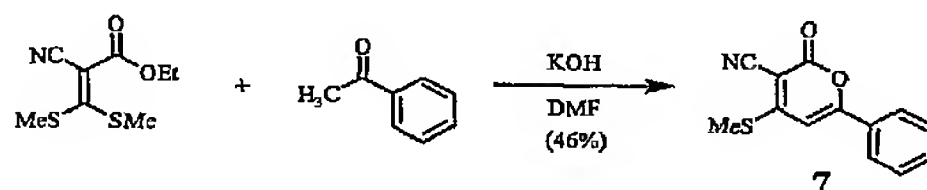
5 1-Benzyl-6-(3-bromomethyl-phenyl)-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile

¹H-NMR (CDCl₃): δ 7.56 (m), 7.45 (m, 1 H), 7.25 (m, 3 H), 7.15 (m, 2 H), 6.88 (m, 2 H), 6.40 (s, 1 H), 5.24 (s, 2 H), 4.39 (s, 2 H).

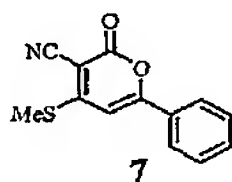
EXAMPLE 7

10

This example illustrates the preparation of compound 7.



3,3-Bis(methylthio)-2-cyanoacrylic acid ethyl ester (2.0 g, 9.2
mmoles – TCI America) was combined with acetophenone (1.1 mL, 9.4
mmoles) in 100 mL of DMF within a round-bottom flask. To this stirring
15 mixture at room temp was then added potassium hydroxide (1.0 g, 17.8
mmoles), and the reaction was stirring at this temp for 12 hours. After this
period the reaction was combined with 150 mL of ice-water and the mixture
was stirred for 2 hours. The resulting heterogeneous mixture was vacuum
filtered, and the yellow filter cake was washed with water and dried to yield
20 product 1.04 g (46% yield) as a yellow solid.

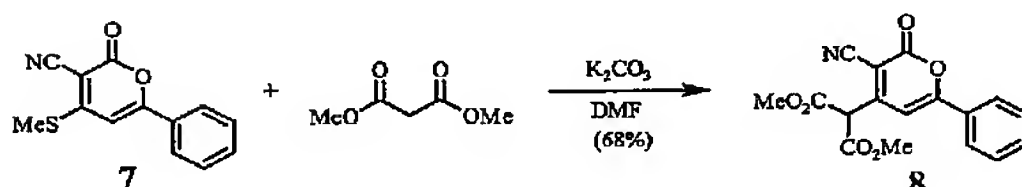


-233-

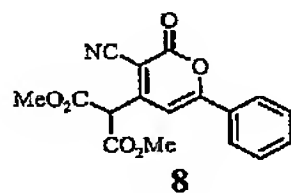
$^1\text{H-NMR}$ (CDCl_3): δ 7.88 (dt, $J'=7.0\text{Hz}$, $J''=1.5\text{Hz}$, 2H), 7.6-7.49 (m, 3H), 6.72 (s, 1H), 2.73 (s, 3H).

EXAMPLE 8

5 This example illustrates the preparation of compound 8.



4-Methylsulfanyl-2-oxo-6-phenyl-2H-pyran-3-carbonitrile, 7 (0.11 g, 0.46 mmoles) was combined with dimethyl malonate (0.11 mL, 0.96 mmoles) and potassium carbonate (0.16 g, 1.2 mmoles) in 2.3 mL of anhydrous DMF. The reaction was stirred at room temp for 12 hours. After this period the mixture was combined with water and 1N HCl (to adjust pH < 6) and was extracted with EtOAc (2 x 30 mL). The resulting organic layer was then washed with sat'd NaCl and was dried over anhydrous Na2SO4. The EtOAc layer was evaporated *in vacuo* to yield the crude product, which was purified using flash silica chromatography to yield product 0.103 g (68% yield) as a yellow solid.



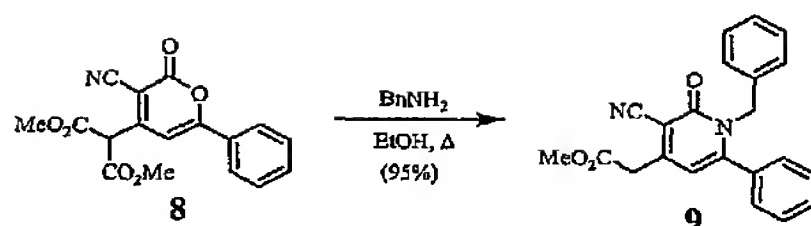
$^1\text{H-NMR}$ (CDCl_3): δ 7.90 (dt, $J'=7.1\text{Hz}$, $J''=1.8\text{Hz}$, 2H), 7.60-7.49 (m, 3H), 7.14 (s, 1H), 5.06 (s, 1H), 3.86 (s, 6H).

20

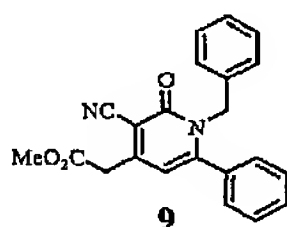
EXAMPLE 9

This example illustrates the preparation of compound 9.

-234-

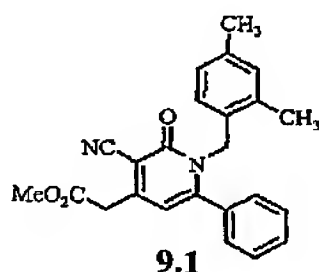


2-(3-Cyano-2-oxo-6-phenyl-2H-pyran-4-yl)-malonic acid dimethyl ester, **8** (26 mg, 0.079 mmoles) was combined with benzylamine (10 μ L, 0.092 mmoles) and 1.0 mL of ethanol within a screw cap vial. The mixture
5 was heated to 80 °C and was stirred at this temp for 2 hours. After this period the mixture was evaporated *in vacuo* and was purified directly by flash silica chromatography (0-50% EtOAc/Hexane) to yield product 27 mg (95% yield) as a beige solid.



10 $^1\text{H-NMR}$ (CDCl_3): δ 7.5-7.44 (m, 1H), 7.38 (t, $J=8.1\text{Hz}$, 2H), 7.22-7.17 (m, 3H), 7.15 (d, $J=7.3\text{Hz}$, 2H), 6.91-6.85 (m, 2H), 6.31 (s, 1H), 5.19 (s, 2H), 3.96 (s, 3H), 3.86 (s, 2H). MS (ES^+): 358.8 (M^+H).

The following compounds were prepared in a manner similar to that described above.

**15**

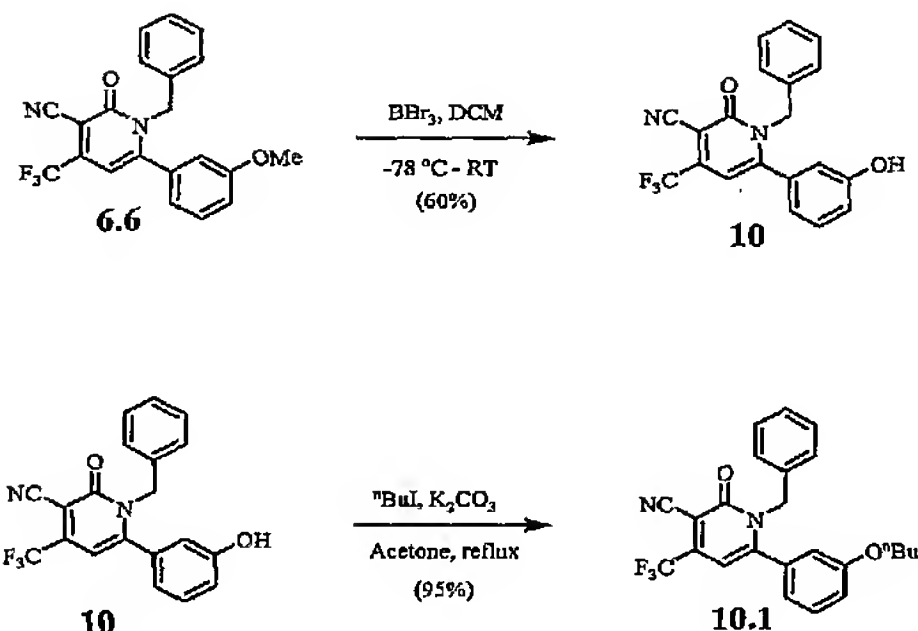
[3-Cyano-1-(2,4-dimethyl-benzyl)-2-oxo-6-phenyl-1,2-dihydro-pyridin-4-yl]-acetic acid methyl ester

$^1\text{H-NMR}$ (CDCl_3): δ 7.28-7.20 (m, 2H), 6.96-6.90 (m, 2H), 6.89-6.82 (m, 2H), 6.67 (s, 1H), 6.62 (d, $J=7.8\text{Hz}$, 1H), 5.09 (s, 2H), 4.01 (s, 3H), 2.27 (s, 3H), 2.25 (s, 3H), 1.88 (s, 3H).

EXAMPLE 10

-235-

This example illustrates the preparation of compound **10.1**.



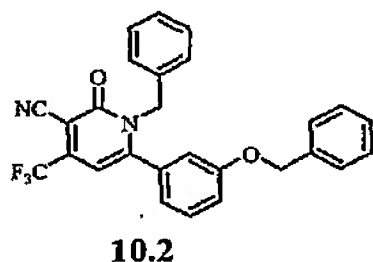
- A solution of boron tribromide (4.5 mL, 47.9 mmol) in 10 mL anhydrous THF was slowly added to a solution of 1-benzyl-3-cyano-6-(3-methoxyphenyl)-4-trifluoromethyl-1H-pyridin-2-one (**6.6**) (8.37 g, 21.8 mmol) in 62 mL of anhydrous THF at $-78\text{ }^\circ\text{C}$ under nitrogen. The mixture was vigorously stirred and allowed to warm to ambient temperature overnight. The mixture was then cooled to $0\text{ }^\circ\text{C}$ with an ice/water bath and to it was added 100 mL of MeOH in portion. The mixture was stirred at room temperature for 1 h and concentrated *in vacuo*. The residue was dissolved in dichloromethane and neutralized to pH 7 by adding 1 N NaOH. The organic layer was washed with water, separated and dried with anhydrous MgSO_4 . The dichloromethane was concentrated *in vacuo*. The resulting crude product was purified by column chromatography (50% EtOAc/hexane), providing a bright yellow solid (**10**) (4.8 g, 60% yield). $^1\text{H-NMR}$ (DMSO-d_6): δ 10.01 (s, 1H), 7.37 (m, 4H), 7.11 (m, 2H), 7.03 (m, 1H), 6.91 (m, 2H), 6.82 (s, 1H), 5.28 (s, 2H).

- To a solution of 1-benzyl-3-cyano-6-(3-hydroxyphenyl)-4-trifluoromethyl-1H-pyridin-2-one (**10**) (98 mg, 0.27 mmol) in 4 mL of acetone was added 1-iodobutane (59 mg, 0.32 mmol) and K_2CO_3 (41 mg, 0.32 mmol). The mixture was stirred and heated to reflux overnight. The salt was removed by filtration

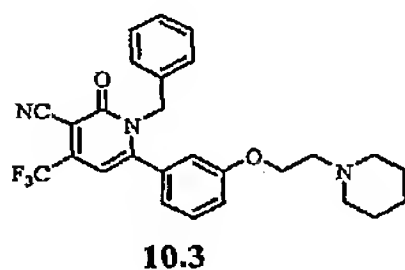
-236-

and the solvent was concentrated *in vacuo*. The resulting crude product was purified by column chromatography (25% EtOAc/hexane), providing a yellow solid (10.1) (107 mg, 95% yield). ¹H-NMR (CDCl₃): δ 7.34 (m, 1H), 7.25 (m, 3H), 7.03 (m, 1H), 6.93 (m, 2H), 6.77 (m, 1H), 6.59 (m, 1H), 6.41 (s, 1H), 5.25 (s, 2H), 3.73 (m, 2H), 1.71 (m, 2H), 1.45 (m, 2H), 0.96 (t, J = 7.3 Hz, 3H).

The following compounds were prepared in a manner similar to that described above.

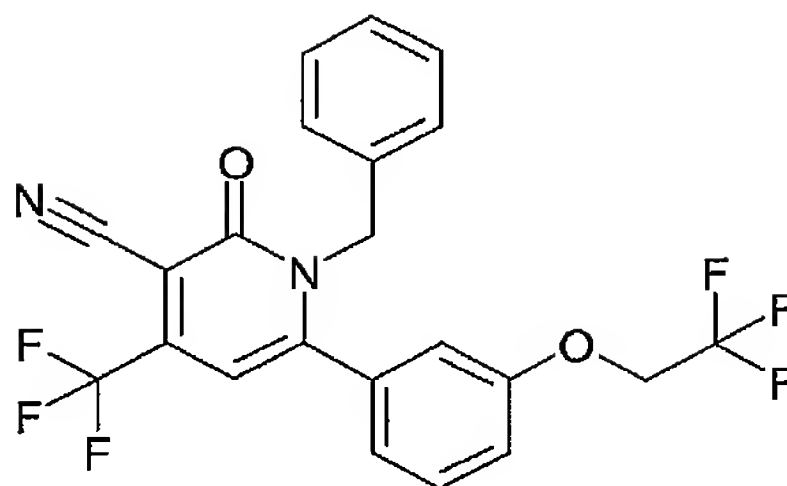


¹H-NMR (CDCl₃): δ 7.44 - 7.33 (m, 6H), 7.26 (m, 3H), 7.12 (m, 1H), 6.90 (m, 2H), 6.79 (m, 1H), 6.68 (m, 1H), 6.40 (s, 1H), 5.21 (s, 2H), 4.68 (s, 2H).



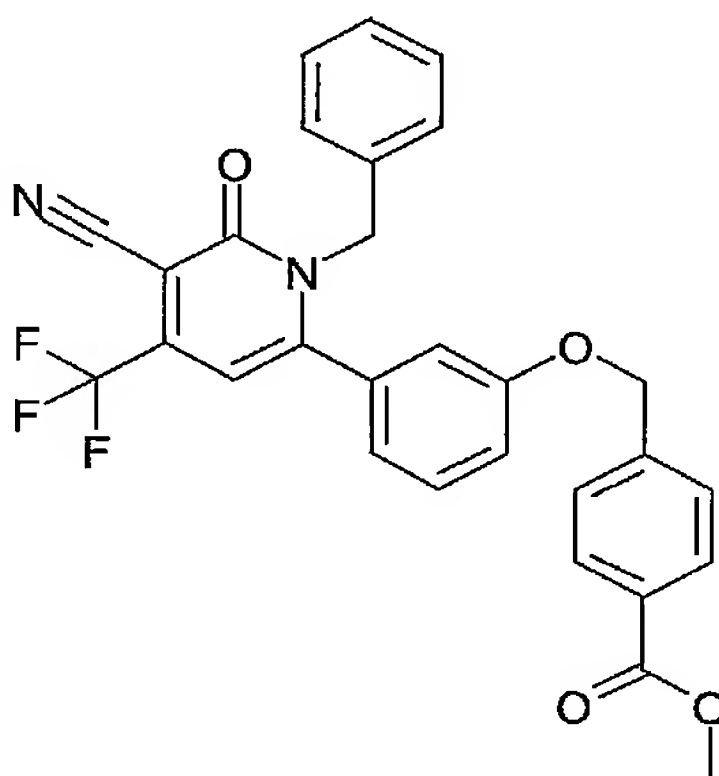
¹H-NMR (CDCl₃): δ 7.34 (m, 1H), 7.24 (m, 3H), 7.06 (m, 1H), 6.92 (m, 2H), 6.77 (m, 1H), 6.64 (m, 1H), 6.40 (s, 1H), 5.25 (s, 2H), 3.91 (t, J = 6.1 Hz, 2H), 2.72 (t, J = 6.1 Hz, 2H), 2.48 (m, 4H), 1.61 (m, 4H), 1.45 (m, 2H).

-237-



10.4

- 1-Benzyl-2-oxo-6-[3-(2,2,2-trifluoro-ethoxy)-phenyl]-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile ¹H-
- 5 NMR (CDCl₃): δ7.45 (m, 1 H), 7.25 (m, 4 H), 7.01 (m, 1 H), 6.88 (m, 3 H), 6.40 (s, 1 H), 5.33 (m, 2 H), 5.26 (s, 2 H).

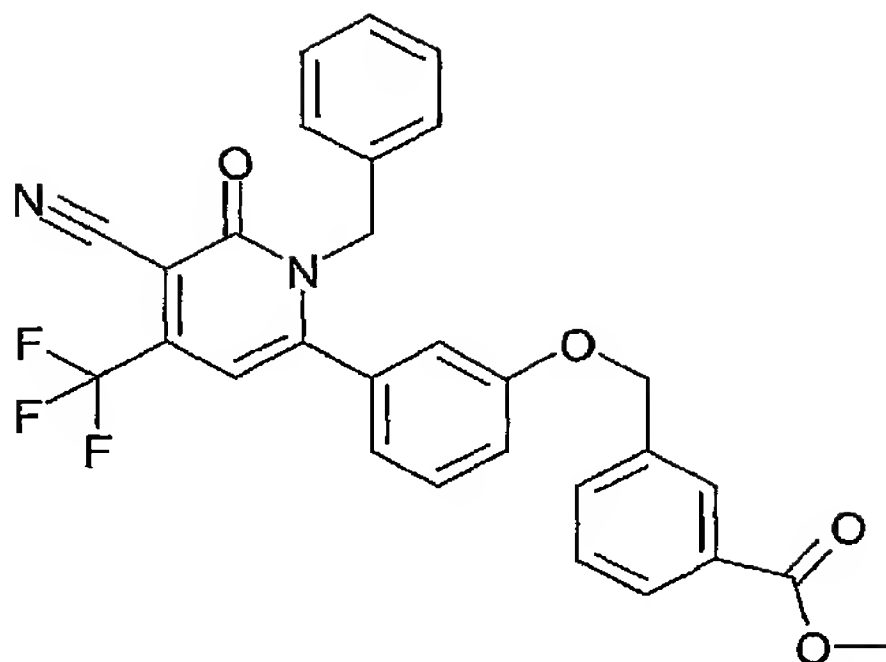


10.5

- 10 4-[3-(1-Benzyl-5-cyano-6-oxo-4-trifluoromethyl-1,6-dihydro-pyridin-2-yl)-phenoxy]methyl-benzoic acid methyl ester ¹H-
- NMR (CDCl₃): δ8.06 (m, 2 H), 7.42 (m, 2 H), 7.36 (m, 1 H), 7.26 (m, 4 H), 7.11 (m, 1 H), 6.92 (m, 2 H), 6.82 (m, 1 H), 6.66 (m, 1 H), 6.40 (s, 1 H), 5.21 (s, 2 H), 4.89 (s, 2 H), 3.93 (s, 3 H)..

-238-

XCT0265953



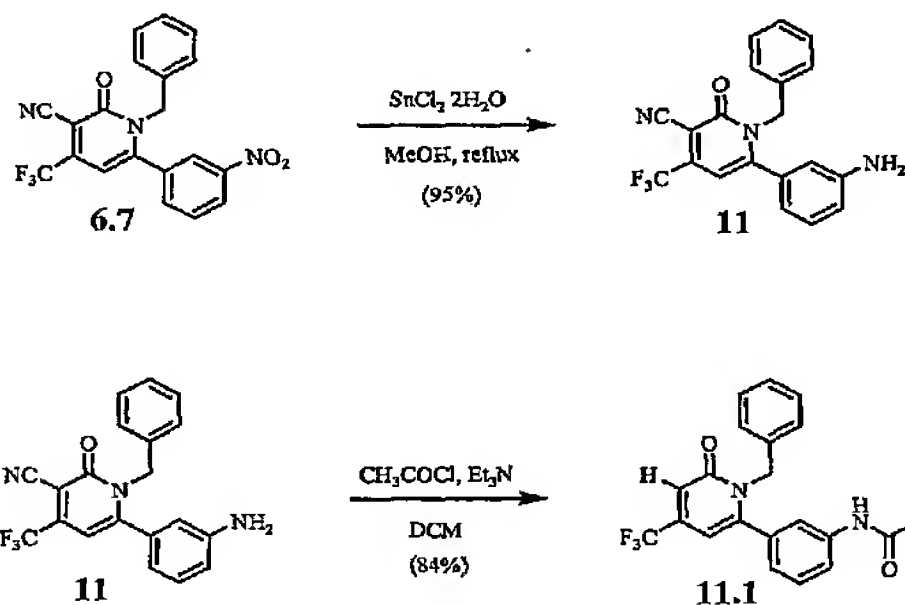
10.6

- 5 3-[3-(1-Benzyl-5-cyano-6-oxo-4-trifluoromethyl-1,6-dihydro-pyridin-2-yl)-
phenoxy]methyl-benzoic acid methyl ester ¹H-
NMR (CDCl₃): δ8.03 (m, 2 H), 7.56 (m, 1 H), 7.48 (m, 1 H), 7.37 (m, 1 H), 7.26
(m, 2 H), 7.11 (m, 1 H), 6.91 (m, 2 H), 6.82 (m, 1 H), 6.67 (m, 1 H), 6.40 (s, 1
H), 5.22 (s, 2 H), 4.87 (s, 2 H), 3.94 (s, 3 H).

10

EXAMPLE 11

This example illustrates the preparation of compound 11.1.



- 15 To a solution of 1-benzyl-3-cyano-6-(3-nitrophenyl)-4-trifluoromethyl-1H-
pyridin-2-one (6.7) (200 mg, 0.50 mmol) in 5 mL of MeOH was added

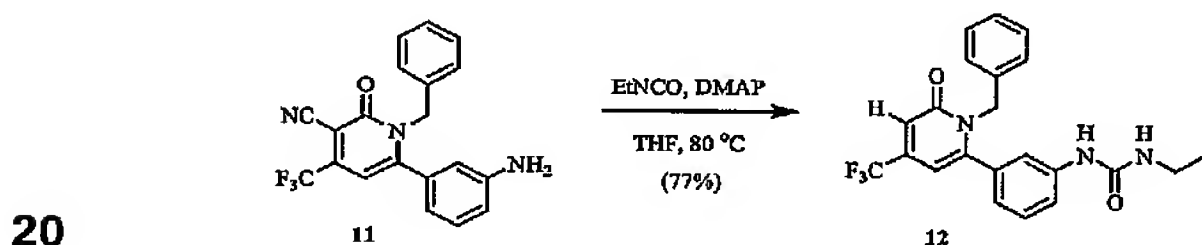
-239-

stannous (II) chloride dihydrate (565 mg, 2.5 mmol). The mixture was stirred and heated to reflux for 3 h. The mixture was then concentrated *in vacuo*. The residue was taken in a mixture of ethyl acetate and 5% aqueous NaHCO₃. The mixture was stirred for 1 h, and the organic layer was separated and the aqueous layer was extracted with ethyl acetate twice. The combined organic layer was dried with anhydrous MgSO₄ and concentrated *in vacuo*. The crude product (**11**) was relatively pure by analysis of its ¹H NMR spectrum and was used for the next reaction without further purification.

To a solution of 6-(3-aminophenyl)-1-benzyl-3-cyano-4-trifluoromethyl-1H-pyridin-2-one (**11**) (74 mg, 0.20 mmol) in 2 mL of dichloromethane was added acetyl chloride (48 mg, 0.6 mmol) and triethylamine (81 mg, 0.64 mmol). The mixture was refluxed overnight. The salt was removed by filtration and the solvent was concentrated *in vacuo*. The resulting crude product was purified by column chromatography (60% EtOAc/hexane), providing **11.1** as a yellow oil (69 mg, 84% yield). ¹H-NMR (CDCl₃): δ 7.57 (m, 2H), 7.43 (s, 1H), 7.35 (m, 1H), 7.23 (m, 3H), 6.90 (m, 2H), 6.85 (m, 1H), 6.41 (s, 1H), 5.27 (s, 2H), 2.19 (s, 3H).

EXAMPLE 12

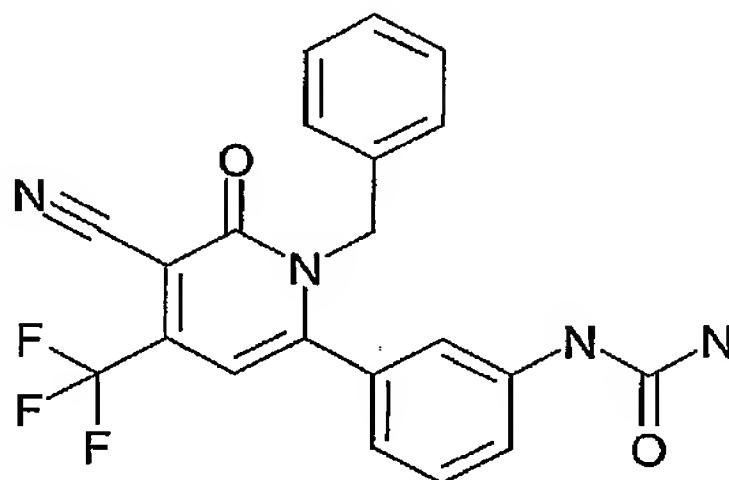
This example illustrates the preparation of compound **12**.



To a solution of 6-(3-aminophenyl)-1-benzyl-3-cyano-4-trifluoromethyl-1H-pyridin-2-one (**11**) (94 mg, 0.26 mmol) in 2 mL of anhydrous THF was added ethyl isocyanate (90 mg, 1.3 mmol) and DMAP (6 mg, 0.05 mmol). The mixture was refluxed overnight. The reaction mixture was cooled to room temperature, concentrated *in vacuo*, and the residue purified by column chromatography (50% EtOAc/hexane) providing **12** as a yellow solid (77 mg,

-240-

77% yield). $^1\text{H-NMR}$ (CDCl_3): δ 7.44 (m, 2H), 7.25 (m, 1H), 7.21 (m, 4H), 6.89 (m, 3H), 6.69 (m, 1H), 6.43 (s, 1H), 5.27 (s, 2H), 3.28 (q, $J = 7.3$ Hz, 2H), 1.16 (t, $J = 7.3$ Hz, 3H).

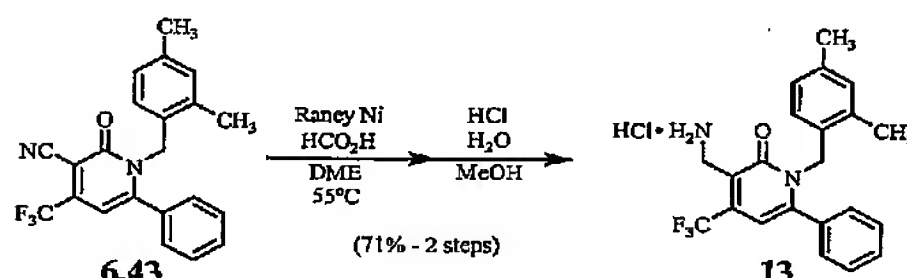


5 [3-(1-Benzyl-5-cyano-6-oxo-4-trifluoromethyl-1,6-dihydro-pyridin-2-yl)-phenyl]-urea

$^1\text{H-NMR}$ (DMSO-d_6): δ 10.20 (s, 1 H), 9.04 (s, 1 H), 7.65 (m, 1 H), 7.58 (m, 1 H), 7.43 (m, 1 H), 7.29 (m, 3 H), 7.07 (m, 1 H), 7.02 (m, 2 H), 6.80 (s, 1 H), 5.23 (s, 2 H).

EXAMPLE 13

This example illustrates the preparation of compound 13.



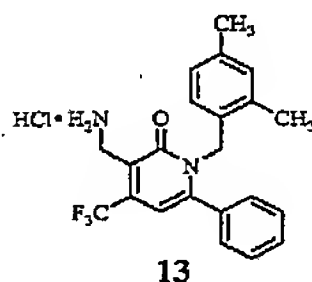
15 Within a 100 mL flask was placed Raney[®]-type Alloy (Aluminum-nickel catalyst, Aldrich, 2.0 g), a magnetic stir bar and 2N NaOH solution (20 mL). The flask was submerged into a water bath at ambient temperature and the mixture was vigorously stirred for 45 min (bubbling occurs). In a separate pear-shaped flask was placed 1-(2,4-Dimethyl-benzyl)-2-oxo-6-phenyl-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile **6.43** (100 mg, 0.26 mmoles) and this was dissolved within formic acid (5 mL) and ethylene glycol dimethyl ether (DME, 1.0 mL). After Ra-Ni activation was complete the hydroxide

-241-

mixture (heterogeneous) was carefully decanted, washed with water, and sequentially decanted to remove the residual sodium hydroxide. Excess water was removed from the activated Ra-Ni using a pipette. The nitrile solution was carefully added to the stirring Ra-Ni at room temperature, and

5 mixture was heated to 55 °C for 3 hours. After this period the reaction mixture was filtered through Celite (with MeOH washings) and concentrated *in vacuo*. The residue was taken up in ethyl acetate and was washed with 50% v/v aqueous NH₄OH (3x20 mL) and brine. The resulting EtOAc solution was dried over anhydrous Na₂SO₄ and was concentrated *in vacuo* to yield crude

10 product as a yellow residue. The crude product was purified using flash silica chromatography (0-10% MeOH/DCM) to yield the free base as a yellow residue. The free base was combined with 2N HCl/MeOH and evaporated to yield the hydrochloride salt. The salt was dissolved in deionized water and freeze-dried to yield 79mg (71% yield) of product 13 as a yellowish powder.

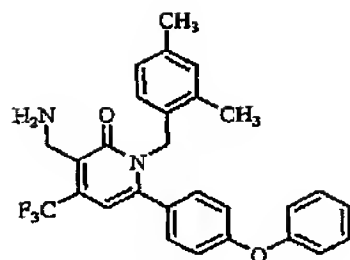


15 (3-Aminomethyl-1-(2,4-dimethyl-benzyl)-6-phenyl-4-trifluoromethyl-1H-pyridin-2-one hydrochloride)

¹H-NMR (CDCl₃): δ (d6-DMSO) 8.38 (bs, 3H), 7.47 (t, J=7.5Hz, 1H), 7.40 (t, J=7.6Hz, 2H), 7.26 (d, J=7.6Hz, 2H), 6.92-6.89 (m, 2H), 6.65 (d, J=7.6Hz, 1H), 6.54 (s, 1H), 5.05 (s, 2H), 4.02 (bs, 2H), 2.21 (s, 3H), 1.87 (s, 3H). MS(ES⁺): 386.9 (M+H)

20 The following compound was prepared in a manner similar to that described above.

-242-



13.2

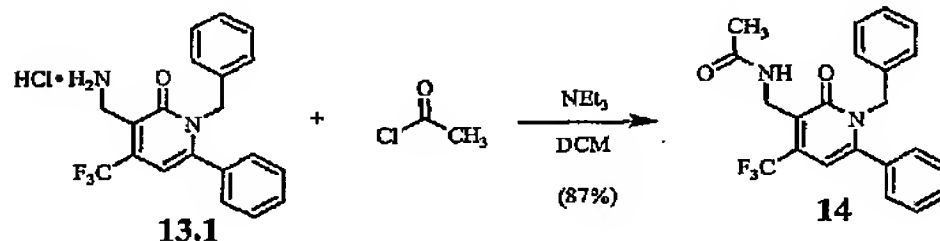
(3-Aminomethyl-1-(2,4-dimethyl-benzyl)-6-(4-phenoxy-phenyl)-4-trifluoromethyl-1H-pyridin-2-one)

$^1\text{H-NMR}$ (CDCl_3): δ 7.20-7.14 (m, 1H), 7.11-6.99 (m, 5H), 6.94-6.87 (m, 5H), 6.58 (d, $J=7.3\text{Hz}$, 1H), 6.34 (s, 1H), 5.09 (s, 2H), 3.93 (s, 2H), 2.26 (s, 3H), 2.01 (s, 3H).

5

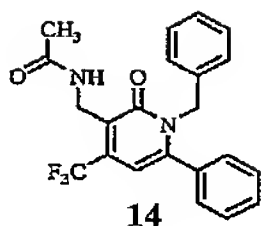
EXAMPLE 14

This example illustrates the preparation of compound **14**.



- 10** 3-Aminomethyl-1-(2,4-dimethyl-benzyl)-6-phenyl-4-trifluoromethyl-1H-pyridin-2-one hydrochloride **13.1** (15 mg, 0.039 mmoles) was combined with acetyl chloride (5 μL , 0.070 mmoles) and triethylamine (12 μL , 0.086 mmoles) in 5 mL of anhydrous DCM within a round-bottom flask. The mixture was stirred at room temperature for 10 hours and was evaporated *in vacuo* to yield
- 15** crude product as a yellow residue. The crude product was purified using flash silica chromatography (0-30% EtOAc /Hexane) to yield 15mg (87% yield) of **14** as a white solid.

-243-



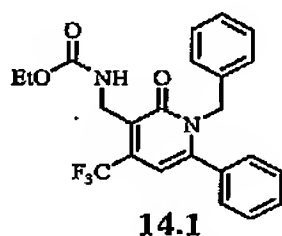
N-(1-Benzyl-2-oxo-6-phenyl-4-trifluoromethyl-1,2-dihydro-pyridin-3-ylmethyl)-acetamide

$^1\text{H-NMR}$ (CDCl_3): δ 7.50-7.43 (m, 1H), 7.38 (t, $J=7.8\text{Hz}$, 2H), 7.25-7.21 (m, 3H), 7.19-7.14 (m, 2H), 6.92-6.85 (m, 2H), 6.83-6.75 (m, 1H), 6.36 (s, 1H), 5.21 (bs, 2H), 4.62 (d, $J=6.1\text{Hz}$, 2H), 1.97 (s, 3H).

5

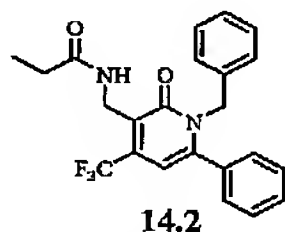
MS(ES⁺): 401.2 (M+H)

The following compounds were prepared in a manner similar to that described above.



(1-Benzyl-2-oxo-6-phenyl-4-trifluoromethyl-1,2-dihydro-pyridin-3-ylmethyl)-carbamic acid ethyl ester

MS(ES⁺): 431.1 (M+H)

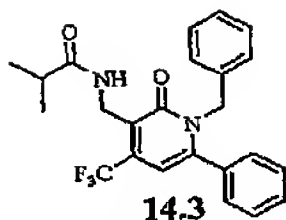


N-(1-Benzyl-2-oxo-6-phenyl-4-trifluoromethyl-1,2-dihydro-pyridin-3-ylmethyl)-propionamide

10

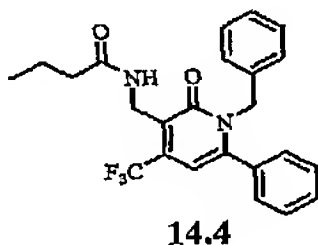
MS(ES⁺): 415.2 (M+H)

-244-



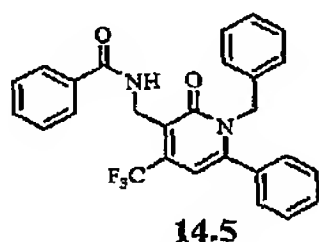
N-(1-Benzyl-2-oxo-6-phenyl-4-trifluoromethyl-1,2-dihydro-pyridin-3-ylmethyl)-isobutyramide

MS(ES⁺): 429.3 (M+H)



N-(1-Benzyl-2-oxo-6-phenyl-4-trifluoromethyl-1,2-dihydro-pyridin-3-ylmethyl)-butyramide

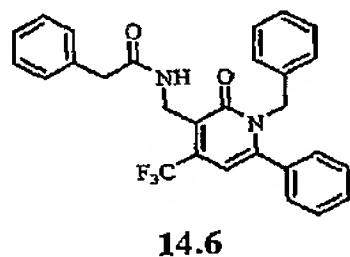
MS(ES⁺): 429.2 (M+H)



N-(1-Benzyl-2-oxo-6-phenyl-4-trifluoromethyl-1,2-dihydro-pyridin-3-ylmethyl)-benzamide

5

MS(ES⁺): 463.2 (M+H)



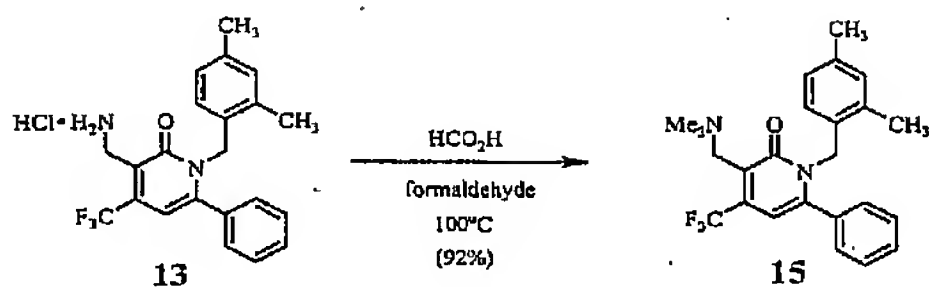
N-(1-Benzyl-2-oxo-6-phenyl-4-trifluoromethyl-1,2-dihydro-pyridin-3-ylmethyl)-2-phenyl-acetamide

MS(ES⁺): 477.1 (M+H)

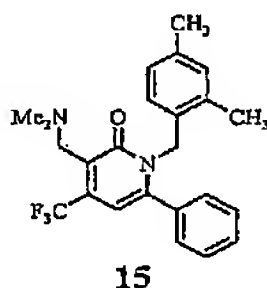
EXAMPLE 15

-245-

This example illustrates the preparation of compound **15**.



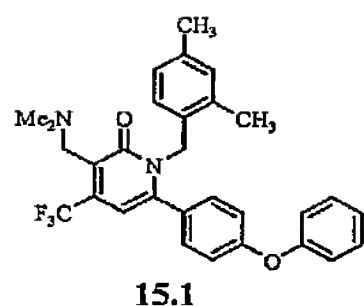
3-Aminomethyl-1-(2,4-dimethyl-benzyl)-6-phenyl-4-trifluoromethyl-1H-pyridin-2-one hydrochloride **13** (39 mg, 0.092 mmoles) was combined with formic acid (96%, 1.0 mL) in 3.0 mL of aqueous formaldehyde (37 wt. % solution in water), and the mixture was stirred at 100 °C for 16 hours. After this period the mixture was poured into a saturated NaHCO₃ solution (20 mL) which was extracted with copious Et₂O. The combined ether layer was washed with brine, dried over anhydrous Na₂SO₄, and was evaporated *in vacuo* to yield crude product as a yellowish residue. The crude product was purified using flash silica chromatography (0-10% MeOH/DCM w/0.1% diethylamine) to yield 35 mg (92% yield) of **15** as a yellowish residue.



(3-Dimethylaminomethyl-1-(2,4-dimethyl-benzyl)-6-phenyl-4-trifluoromethyl-1H-pyridin-2-one)

¹H-NMR (CDCl₃): δ 7.43-7.37 (m, 1H), 7.31 (t, J=7.8Hz, 2H), 7.17-7.11 (m, 2H), 6.89 (bd, J=7.8Hz, 1H), 6.85 (bs, 1H), 6.56 (d, J=7.8Hz, 1H), 6.32 (s, 1H), 5.07 (s, 2H), 3.63-3.59 (m, 2H), 2.36 (s, 6H), 2.25 (s, 3H), 1.92 (s, 3H). MS(ES⁺): 415.4 (M+H)

-246-

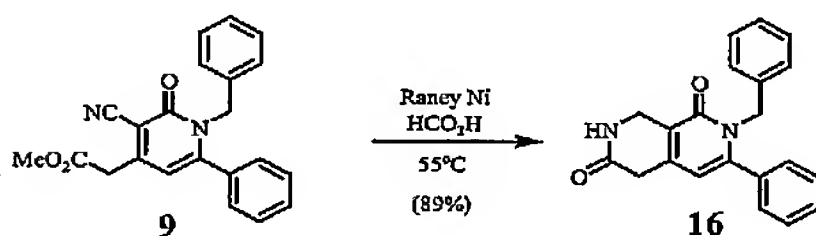


3-Dimethylaminomethyl-1-(2,4-dimethyl-benzyl)-6-(4-phenoxy-phenyl)-4-trifluoromethyl-1H-pyridin-2-one

MS(ES⁺): 507.2 (M+H)

EXAMPLE 16

This example illustrates the preparation of compound 16.



5

Within a 100 mL flask was placed Raney[®]-type Alloy (Aluminum-nickel catalyst, Aldrich, 4.0 g), a magnetic stir bar and 2N NaOH solution (50 mL). The flask was submerged into a water bath at ambient temperature and the mixture was vigorously stirred for 45 min (bubbling occurs). In a separate

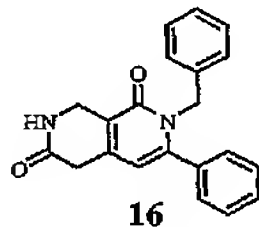
10 pear-shaped flask was placed [3-Cyano-1-(2,4-dimethyl-benzyl)-2-oxo-6-phenyl-1,2-dihydro-pyridin-4-yl]-acetic acid methyl ester **9** (183 mg, 0.46 mmoles) and this was dissolved within formic acid (8 mL). After Ra-Ni activation was complete the hydroxide mixture (heterogeneous) was carefully decanted, washed with water, and sequentially decanted to remove the

15 residual sodium hydroxide. Excess water was removed from the activated Ra-Ni using a pipette. The nitrile solution was carefully added to the stirring Ra-Ni at room temperature, and mixture was heated to 55 °C for 90 min. After this period the reaction mixture was filtered through Celite (with MeOH washings) and concentrated *in vacuo*. The residue was taken up in EA and

20 was washed with 50% v/v aqueous NH₄OH (3x20 mL) and brine. The

-247-

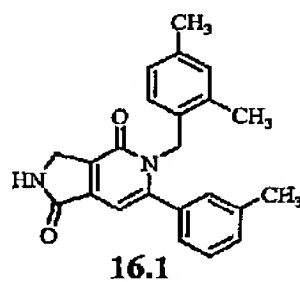
resulting EA solution was dried over anhydrous Na_2SO_4 and was concentrated *in vacuo* to yield 0.151 g (89% yield) of **16** as a yellow residue.



16
2-Benzyl-3-phenyl-7,8-dihydro-2H,5H-[2,7]naphthyridine-1,6-dione

5 $^1\text{H-NMR}$ (CDCl_3): δ 7.48-7.41 (m, 1H), 7.40-7.33 (m, 2H), 7.20-7.09 (m, 5H), 6.95-6.89 (m, 2H), 5.95 (s, 1H), 5.84 (bs, 1H), 5.20 (bs, 2H), 3.55-3.47 (m, 2H), 2.81 (t, $J=6.6\text{Hz}$, 2H). $\text{MS(ES}^+)$: 331.2 (M^+H)

The following compound was prepared in a manner similar to that described above.

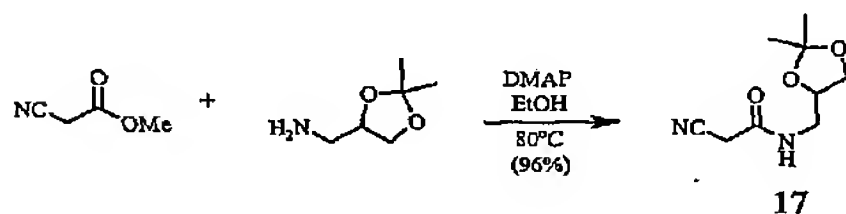


16.1
5-(2,4-Dimethyl-benzyl)-6-*m*-tolyl-3,5-dihydro-2H-pyrrolo[3,4-*c*]pyridine-1,4-dione

10 $\text{MS(ES}^+)$: 359.2 (M^+H)

EXAMPLE 17

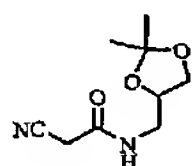
This example illustrates the preparation of compound **17**.



15 Methyl cyanoacetate (6.7 mL, 75.9 mmoles) was combined with 2,2-dimethyl-1,3-dioxolane-4-methanamine (4.6 g, 50.5 mmoles), 4-(*N,N*-dimethylamino)pyridine (20 mg, 0.16 mmoles) and 20 mL of Ethanol within a

-248-

round-bottom flask. The mixture was then stirred at 80 °C for 16 hours. After this period reaction mixture was evaporated *in vacuo* and was purified using flash silica chromatography (0-60% EtOAc/hexane) to yield 7.33 g (96% yield) of **17** as a yellowish liquid.



17
2-Cyano-N-(2,2-dimethyl-[1,3]dioxolan-4-ylmethyl)-acetamide

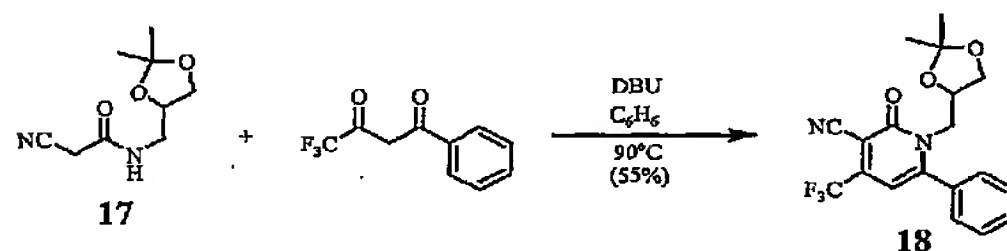
5

¹H-NMR (CDCl₃): δ 6.43 (bs, 1H), 4.31-4.21 (m, 1H), 4.10-4.04 (m, 1H), 3.65 (dd, J'=8.3Hz, J''=5.8Hz, 1H), 3.59 (dq, J¹=13.9Hz, J²=5.6Hz, J³=3.5Hz, 1H), 3.41 (s, 2H), 3.39-3.33 (m, 1H), 1.47 (s, 3H), 1.36 (s, 3H).

10

EXAMPLE 18

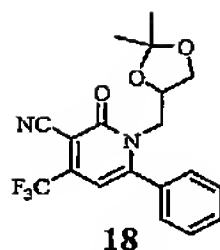
This example illustrates the preparation of compound **18**.



2-Cyano-N-(2,2-dimethyl-[1,3]dioxolan-4-ylmethyl)-acetamide **17** (2.05 g, 10.3 mmol), 4,4,4-Trifluoro-1-phenyl-butane-1,3-dione (2.2 g, 10.3 mmol) and DBU (0.77 mL, 5.1 mmol) were combined with 20 mL of benzene within a round-bottom flask. The mixture was stirred at 90 °C for 16 hours. After this period the reaction mix was purified directly using flash silica chromatography (0-40% EtOAc/Hexane) to yield 2.14g (55% yield) of **18** as a yellow residue.

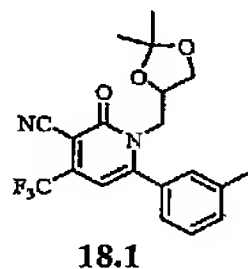
15

-249-



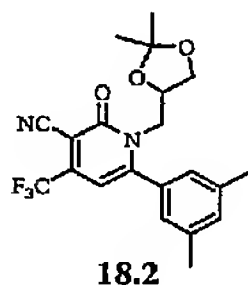
1-(2,2-Dimethyl-[1,3]dioxolan-4-ylmethyl)-2-oxo-6-phenyl-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile.

5 $^1\text{H-NMR}$ (CDCl_3): δ 7.60-7.49 (m, 3H), 7.48-7.37 (m, 2H), 6.42 (s, 1H), 4.59-4.52 (m, 1H), 4.33 (dd, $J'=13.1\text{Hz}$, $J''=2.5\text{Hz}$, 1H), 4.09 (dd, $J'=8.8\text{Hz}$, $J''=6.8\text{Hz}$, 1H), 4.02 (dd, $J'=12.9\text{Hz}$, $J''=8.6\text{Hz}$, 1H), 3.51 (dd, $J'=8.6\text{Hz}$, $J''=6.1\text{Hz}$, 1H), 1.24 (s, 3H), 1.10 (s, 3H). MS(ES⁺): 379.4 (M+H)



1-(2,2-Dimethyl-[1,3]dioxolan-4-ylmethyl)-2-oxo-6-*m*-tolyl-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile

10 $^1\text{H-NMR}$ (CDCl_3): δ 7.43-7.33 (m, 2H), 7.22 (bs, 2H), 6.41 (s, 1H), 4.59-4.51 (m, 1H), 4.34-4.30 (dd, $J'=13.1\text{Hz}$, $J''=2.8\text{Hz}$, 1H), 4.16-4.00 (m, 2H), 3.52 (dd, $J'=8.8\text{Hz}$, $J''=5.8\text{Hz}$, 1H), 2.43 (s, 6H), 1.11 (s, 3H).



1-(2,2-Dimethyl-[1,3]dioxolan-4-ylmethyl)-6-(3,5-dimethyl-phenyl)-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile

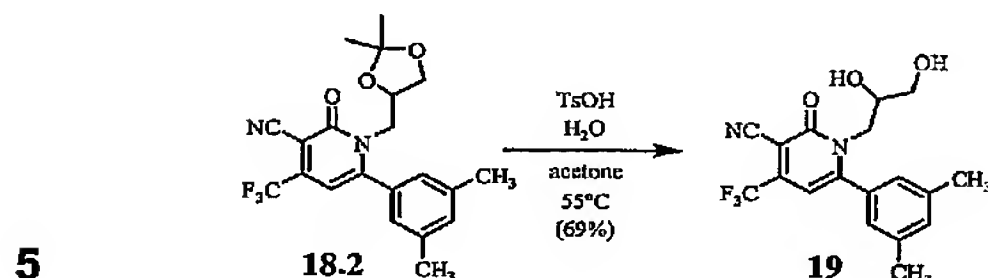
$^1\text{H-NMR}$ (CDCl_3): δ 7.16 (s, 1H), 6.99 (bs, 2H), 6.40 (s, 1H), 4.59-4.52 (m, 1H), 4.34 (dd, $J'=12.9\text{Hz}$, $J''=2.5\text{Hz}$, 1H), 4.13-4.00 (m,

-250-

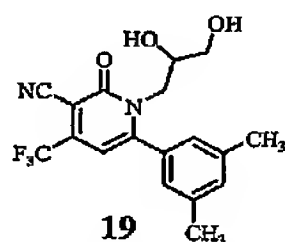
2H), 3.53 (dd, $J'=8.6\text{Hz}$, $J''=6.3\text{Hz}$, 1H), 2.38 (s, 6H), 1.24 (s, 3H), 1.12 (s, 3H).

EXAMPLE 19

This example illustrates the preparation of compound **19**.



10 1-(2,2-Dimethyl-[1,3]dioxolan-4-ylmethyl)-6-(3,5-dimethyl-phenyl)-2-oxo-4-trifluoro-methyl-1,2-dihydro-pyridine-3-carbonitrile **18.2** (0.72 g, 1.78 moles) was combined with p-toluenesulfonic acid monohydrate (0.34 g, 1.78 mmols), water (2 mL) and 30 mL of acetone within a round-bottom flask equipped with a reflux condensor. The mixture was stirred at 55 °C for 3 hours. After this period the reaction mixture was evaporated *in vacuo* and was purified directly using flash silica chromatography (0-80% EtOAc/Hexane) to yield 0.45 g (69% yield) of **19** as a white solid.

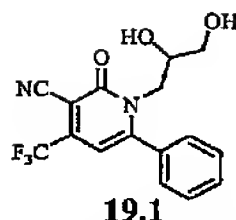


1-(2,3-Dihydroxy-propyl)-6-(3,5-dimethyl-phenyl)-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile

15 $^1\text{H-NMR}$ (CDCl_3): δ 7.19 (s, 1H), 6.95 (s, 2H), 6.46 (s, 1H), 4.24-4.12 (m, 2H), 3.94-3.86 (m, 1H), 3.63-3.55 (m, 1H), 3.43-3.36 (m, 1H), 3.21 (d, $J=6.1\text{Hz}$, 1H), 2.39 (s, 6H).

The following compounds were prepared in a manner similar to that described above.

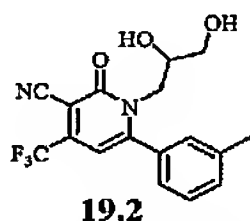
-251-



19.1

1-(2,3-Dihydroxy-propyl)-2-oxo-6-phenyl-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile

MS(ES⁺): 339.1 (M+H)



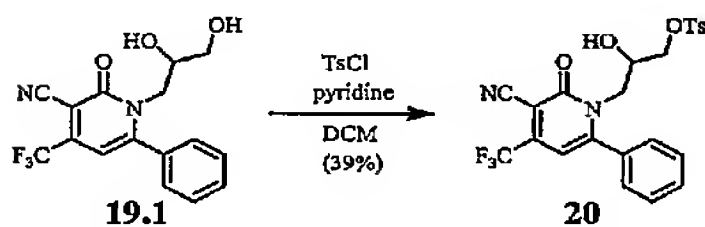
19.2

1-(2,3-Dihydroxy-propyl)-2-oxo-6-*m*-tolyl-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile

5 ¹H-NMR (CDCl₃): δ 7.47-7.33 (m, 2H), 7.21 (bs, 2H), 6.48 (s, 1H), 4.24-4.09 (m, 2H), 4.04-3.97 (m, 1H), 3.56 (dd, J'=11.6Hz, J''=4.0Hz, 1H), 3.37 (dd, J'=11.9Hz, J''=4.8Hz, 1H), 2.82 (bs, 1H), 2.43 (s, 3H).

EXAMPLE 20

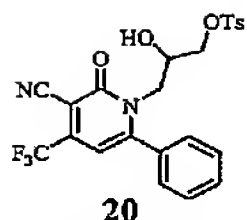
This example illustrates the preparation of compound **20**



10

15 1-(2,3-Dihydroxy-propyl)-2-oxo-6-phenyl-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile **19.1** (0.33 g, 0.98 mmoles) was combined with *p*-toluenesulfonyl chloride (0.2 g, 1.05 mmoles), pyridine (0.1 mL, 1.24 mmoles) and 3 mL of anhydrous DCM within a 7 mL reaction vial. The mixture was then stirred at room temp for 24 hours. After this period the reaction mixture was evaporated *in vacuo* and was purified directly using flash silica chromatography (0-30% EtOAc/Hexane) to yield 186 mg (39% yield) of **20** was a yellow residue.

-252-

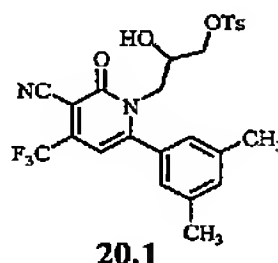


Toluene-4-sulfonic acid 3-(3-cyano-2-oxo-6-phenyl-4-trifluoromethyl-2*H*-pyridin-1-yl)-2-hydroxy-propyl ester

5

¹H-NMR (CDCl₃): δ 7.66 (d, J=8.3Hz, 2H), 7.62-7.52 (m, 3H), 7.44-7.38 (m, 2H), 7.33 (d, J=8.1Hz, 2H), 6.46 (s, 1H), 4.30-4.21 (m, 1H), 4.17-4.07 (m, 2H), 3.97-3.87 (m, 2H), 3.38 (d, J=5.8Hz, 1H), 2.45 (s, 3H).

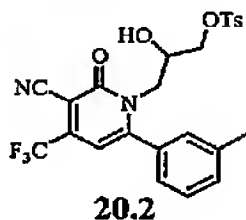
The following compounds were prepared in a manner similar to that described above.



Toluene-4-sulfonic acid 3-[3-cyano-6-(3,5-dimethyl-phenyl)-2-oxo-4-trifluoromethyl-2*H*-pyridin-1-yl]-2-hydroxy-propyl ester

10

¹H-NMR (CDCl₃): δ 7.67 (d, J=8.3Hz, 2H), 7.33 (d, J=8.1Hz, 2H), 7.20 (s, 1H), 6.97 (bs, 2H), 6.45 (s, 1H), 4.23-4.05 (m, 4H), 3.96-3.87 (m, 2H), 3.38-3.34 (m, 1H), 2.45 (s, 3H), 2.40 (s, 6H).



Toluene-4-sulfonic acid 3-(3-cyano-2-oxo-6-*m*-tolyl-4-trifluoromethyl-2*H*-pyridin-1-yl)-2-hydroxy-propyl ester

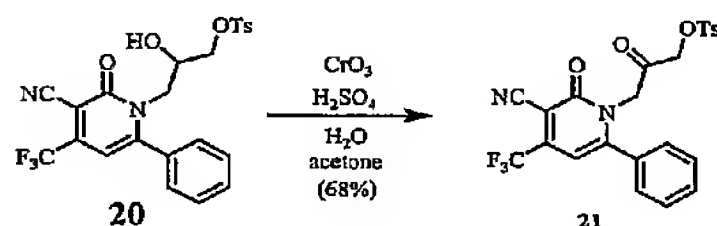
15

¹H-NMR (CDCl₃): δ 7.66 d (J=8.3Hz, 2H), 7.48-7.36 (m, 3H), 7.33 (d, J=8.3Hz, 2H), 7.19 (bs, 2H), 6.45 (s, 1H), 4.25-4.05 (m, 3H), 3.96-3.86 (m, 2H), 3.45 (bs, 1H), 2.45 (s, 3H), 2.44 (s, 3H).

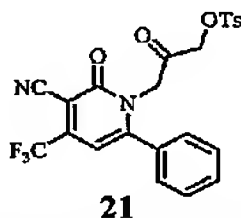
-253-

EXAMPLE 21

This example illustrates the preparation of compound **21**.



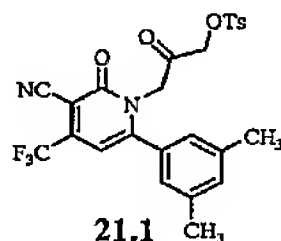
- 5 Toluene-4-sulfonic acid 3-(3-cyano-2-oxo-6-phenyl-4-trifluoromethyl-2H-pyridin-1-yl)-2-hydroxy-propyl ester **20** (46 mg, 0.093 mmoles) was dissolved into acetone. To this solution at room temperature was added 2.67 M Jones Reagent (0.15 mL, 0.40 mmoles) and the resulting mixture was stirred at this temperature for 3 hours. After this period the reaction mixture was gravity filtered through paper, evaporated *in vacuo* and
- 10 was purified directly using flash silica chromatography (0-30% EtOAc/Hexane) to yield 31 mg (68% yield) of **21** as a yellow residue.



Toluene-4-sulfonic acid 3-(3-cyano-2-oxo-6-phenyl-4-trifluoromethyl-2H-pyridin-1-yl)-2-oxo-propyl ester

¹H-NMR (CDCl₃): δ 7.76 (d, J=8.3Hz, 2H), 7.63-7.52 (m, 3H), 7.40-7.32 (m, 4H), 6.50 (s, 1H), 4.84 (s, 2H), 4.59 (s, 2H), 2.47 (s, 3H).

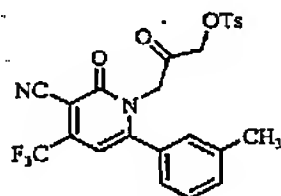
- 15 The following compounds were prepared in a manner similar to that described above.



Toluene-4-sulfonic acid 3-[3-cyano-6-(3,5-dimethyl-phenyl)-2-oxo-4-trifluoromethyl-2H-pyridin-1-yl]-2-oxo-propyl ester

-254-

$^1\text{H-NMR}$ (CDCl_3): δ 7.76 (d, $J=8.3\text{Hz}$, 2H), 7.38 (d, $J=8.3\text{Hz}$, 2H), 7.21 (bs, 1H), 6.93 (s, 2H), 6.48 (s, 1H), 4.86 (s, 2H), 4.60 (s, 2H), 2.47 (s, 3H), 2.38 (s, 6H).



21.2

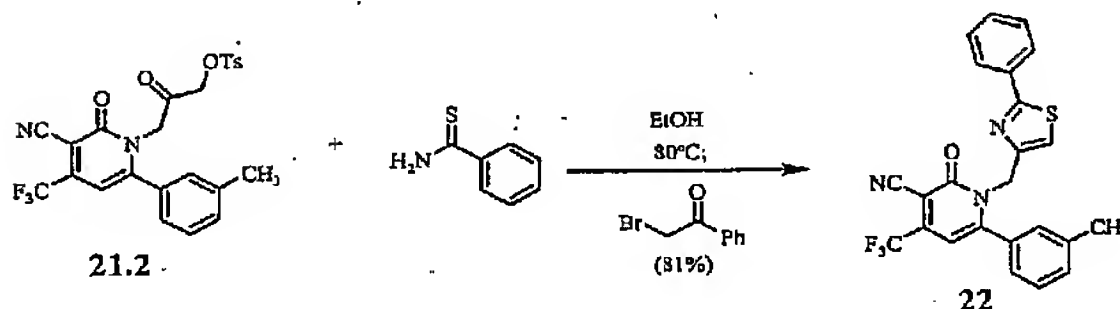
Toluene-4-sulfonic acid 3-(3-cyano-2-oxo-6-m-tolyl-4-trifluoromethyl-2H-pyridin-1-yl)-2-oxo-propyl ester

5

$^1\text{H-NMR}$ (CDCl_3): δ 7.76 (d, $J=8.3\text{Hz}$, 2H), 7.45-7.35 (m, 4H), 7.17-7.10 (m, 2H), 6.49 (s, 1H), 4.85 (s, 2H), 4.59 (s, 2H), 2.47 (s, 3H), 2.43 (s, 3H).

EXAMPLE 22

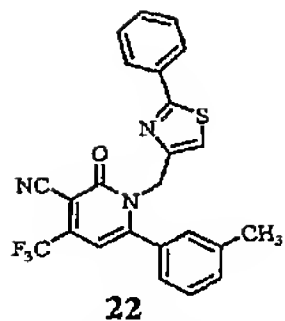
This example illustrates the preparation of compound 22.



10

Toluene-4-sulfonic acid 3-(3-cyano-2-oxo-6-m-tolyl-4-trifluoromethyl-2H-pyridin-1-yl)-2-oxo-propyl ester **21.2** (11 mg, 0.022 mmoles) was combined with thiobenzamide (6 mg, 0.044 mmoles) and 1.0 mL of EtOH within a 7 mL reaction vial. This mixture was stirred at 80 °C for 16 hours. After this period
 15 2-bromoacetophenone (7 mg, 0.035 mmoles) was added and the mixture was stirred at 80 °C for an additional 3 hours. After this period the reaction mixture was evaporated *in vacuo* and was purified using flash silica chromatography (0-20% EtOAc/Hexane) to yield 8mg (81% yield) of **22** as a yellowish residue.

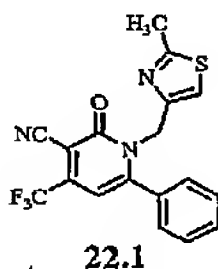
-255-



2-Oxo-1-(2-phenyl-thiazol-4-ylmethyl)-6-*m*-tolyl-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile

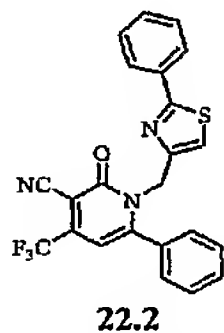
$^1\text{H-NMR}$ (CDCl_3): δ 7.89-7.82 (m, 2H), 7.46-7.34 (m, 7H), 7.30 (s, 1H), 6.44 (s, 1H), 5.28 (s, 2H), 2.41 (s, 3H). MS(ES⁺): 452.1 (M+H)

5 The following compounds were prepared in a manner similar to that described above.



1-(2-Methyl-thiazol-4-ylmethyl)-2-oxo-6-phenyl-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile

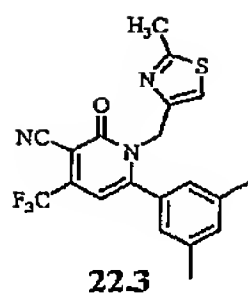
MS(ES⁺): 398.0 (M+Na)



2-Oxo-6-phenyl-1-(2-phenyl-thiazol-4-ylmethyl)-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile

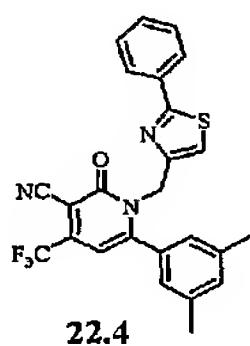
MS(ES⁺): 438.2 (M+H)

-256-



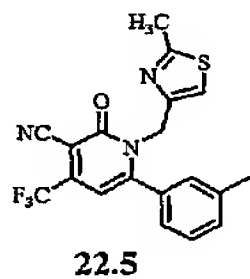
6-(3,5-Dimethyl-phenyl)-1-(2-methyl-thiazol-4-ylmethyl)-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile

MS(ES⁺): 404.1 (M+H)



2-Oxo-1-(2-phenyl-thiazol-4-ylmethyl)-6-*m*-tolyl-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile

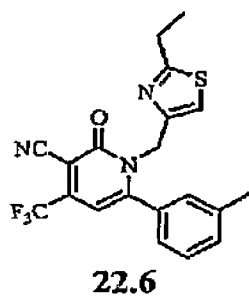
MS(ES⁺): 466.2 (M+H)



1-(2-Methyl-thiazol-4-ylmethyl)-2-oxo-6-*m*-tolyl-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile

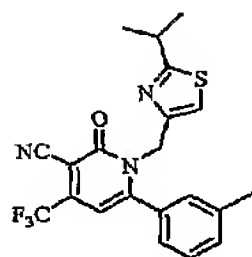
5

MS(ES⁺): 389.8 (M+H)



1-(2-Ethyl-thiazol-4-ylmethyl)-2-oxo-6-*m*-tolyl-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile

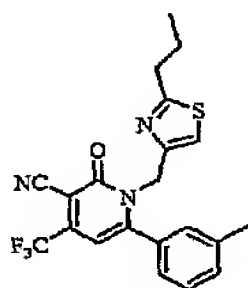
-257-

MS(ES⁺): 404.0 (M+H)

22.7

1-(2-Isopropyl-thiazol-4-ylmethyl)-2-oxo-6-*m*-tolyl-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile

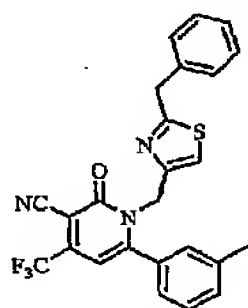
¹H-NMR (CDCl₃): δ 7.39-7.27 (m, 4H), 7.11 (s, 1H), 6.42 (s, 1H), 5.19 (s, 2H), 3.22 (m, J=6.8Hz, 1H), 2.39 (s, 3H), 1.36 (d, J=6.8Hz, 6H).



22.8

2-Oxo-1-(2-propyl-thiazol-4-ylmethyl)-6-*m*-tolyl-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile

5

MS(ES⁺): 418.3 (M+H)

18.9

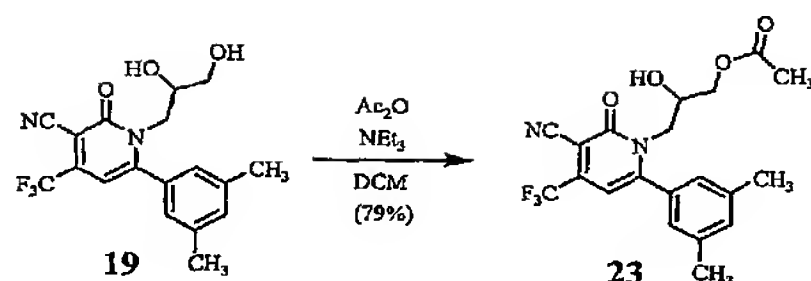
1-(2-Benzyl-thiazol-4-ylmethyl)-2-oxo-6-*m*-tolyl-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile

MS(ES⁺): 466.2 (M+H)**EXAMPLE 23**

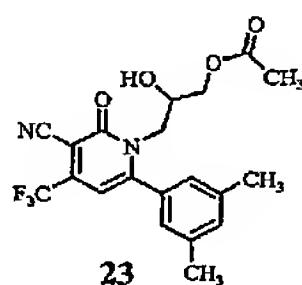
10

This example illustrates the preparation of compound 23.

-258-



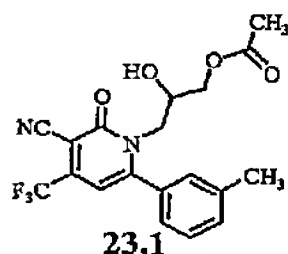
1-(2,3-Dihydroxy-propyl)-6-(3,5-dimethyl-phenyl)-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile **19** (33 mg, 0.09 mmoles) was combined with acetic acid anhydride (9 μ L, 0.095 mmoles), triethylamine (100 μ L, 0.11 mmoles) and 2.0 mL of DCM within a 7 mL reaction vial. This mixture was stirred at room temperature for 24 hours. After this period the reaction mixture was purified directly by flash silica chromatography (0-40% EtOAc/Hexane) to yield 29 mg (79% yield) of **23** as a white solid.



Acetic acid 3-[3-cyano-6-(3,5-dimethyl-phenyl)-2-oxo-4-trifluoromethyl-2H-pyridin-1-yl]-2-hydroxy-propyl ester

10 $^1\text{H-NMR}$ (CDCl_3): δ 7.19 (bs, 1H), 6.98 (bs, 2H), 6.44 (s, 1H), 4.28-3.91 (m, 6H), 3.15 (bs, 1H), 2.39 (s, 6H), 1.94 (s, 3H).

The following compounds were prepared in a manner similar to that described above.



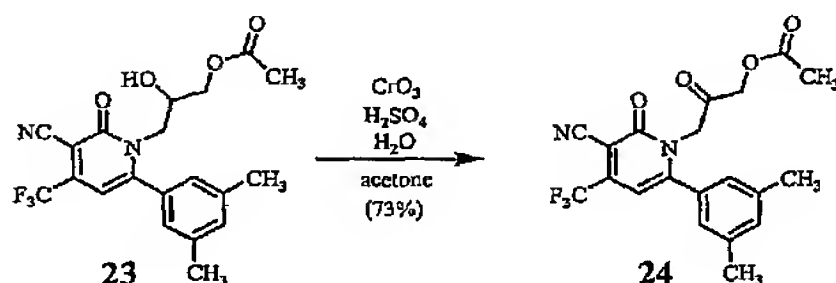
Acetic acid 3-(3-cyano-2-oxo-6-m-tolyl-4-trifluoromethyl-2H-pyridin-1-yl)-2-hydroxy-propyl ester

15 $^1\text{H-NMR}$ (CDCl_3): δ 7.45-7.35 (m, 2H), 7.19 (bs, 2H), 6.45 (s, 1H), 4.27-3.91 (m, 6H), 3.05 (bs, 1H), 2.44 (s, 3H), 1.93 (s, 3H).

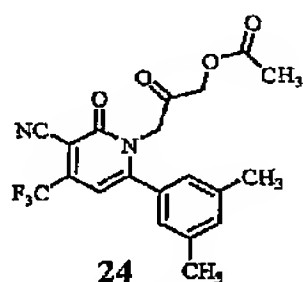
-259-

EXAMPLE 24

This example illustrates the preparation of compound **24**.



- Acetic acid 3-[3-cyano-6-(3,5-dimethyl-phenyl)-2-oxo-4-trifluoromethyl-2H-pyridin-1-yl]-2-hydroxy-propyl ester **23** (29 mg, 0.071 mmols) was dissolved into 3 mL of acetone within a 7 ml reaction vial. To this solution was added 2.67M Jones Reagent (53 mL, 0.142 mmols) and the mixture was stirred at room temperature for 2 hours. After this period the reaction mixture was gravity filtered through paper and the resulting filtrate was evaporated *in vacuo*, and purified using flash silica chromatography (0-40% EtOAc/Hexane) to yield 21 mg (73% yield) of **24** as a white solid.



Acetic acid 3-[3-cyano-6-(3,5-dimethyl-phenyl)-2-oxo-4-trifluoromethyl-2H-pyridin-1-yl]-2-oxo-propyl ester

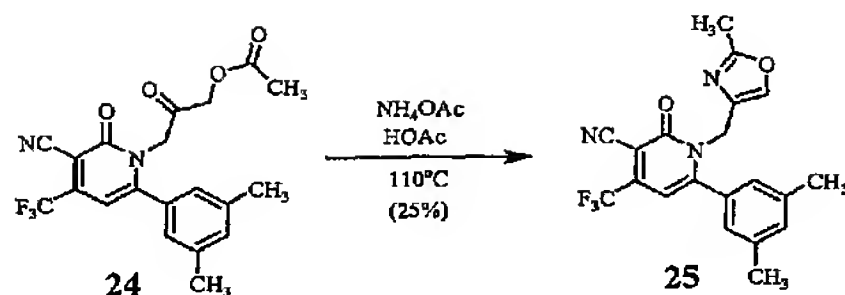
$^1\text{H-NMR}$ (CDCl_3): δ 7.19 (s, 1H), 6.93 (s, 2H), 6.48 (s, 1H), 4.73 (s, 2H), 4.72 (s, 2H), 2.37 (s, 6H), 2.14 (s, 3H).

15

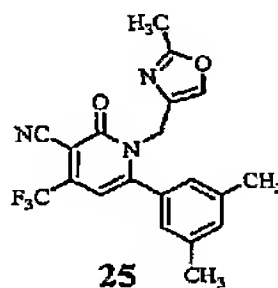
EXAMPLE 25

This example illustrates the preparation of compound **25**.

-260-



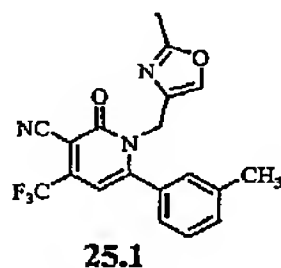
Acetic acid 3-[3-cyano-6-(3,5-dimethyl-phenyl)-2-oxo-4-trifluoromethyl-2H-pyridin-1-yl]-2-oxo-propyl ester **24** (21 mg, 0.052 mmoles) was combined with ammonium acetate (50 mg, 0.64 mmoles) and 1.0 mL of glacial acetic acid within a 7 mL reaction vial, and the mixture was stirred at 110 °C for 16 hours. After this period the reaction mixture was evaporated *in vacuo* and was purified using flash silica chromatography (0-40% EtOAc/Hexane) to yield 5mg (25% yield) of **25** as a white solid.



6-(3,5-Dimethyl-phenyl)-1-(2-methyl-oxazol-4-ylmethyl)-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile

¹H-NMR (CDCl₃): δ 7.59 (s, 1H), 7.19 (bs, 1H), 7.15 (s, 2H), 6.41 (s, 1H), 4.98 (s, 2H), 2.41 (s, 3H), 2.38 (s, 6H).

The following compounds were prepared in a manner similar to that described above.

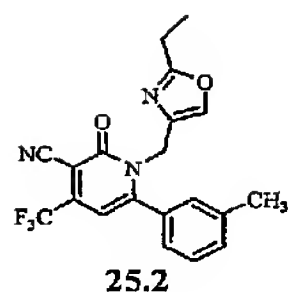


1-(2-Methyl-oxazol-4-ylmethyl)-2-oxo-6-*m*-tolyl-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile

15

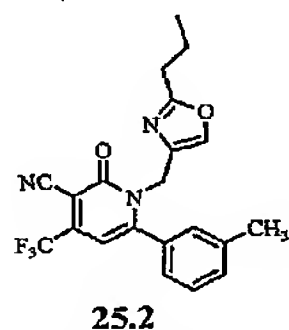
MS(ES⁺): 374.1 (M+H)

-261-



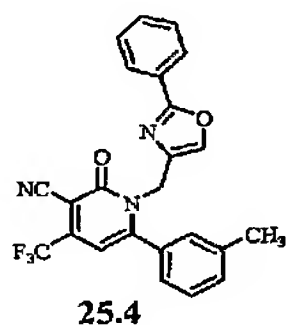
1-(2-Ethyl-oxazol-4-ylmethyl)-2-oxo-
6-*m*-tolyl-4-trifluoromethyl-1,2-
dihydro-pyridine-3-carbonitrile

MS(ES⁺): 388.0 (M+H)



2-Oxo-1-(2-propyl-oxazol-4-ylmethyl)-
6-*m*-tolyl-4-trifluoromethyl-1,2-
dihydro-pyridine-3-carbonitrile

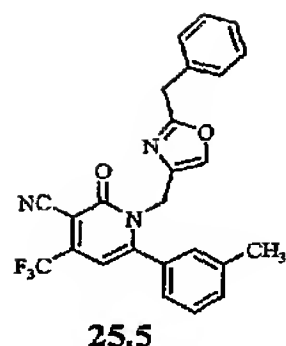
MS(ES⁺): 402.1 (M+H)



2-Oxo-1-(2-phenyl-oxazol-4-ylmethyl)-
6-*m*-tolyl-4-trifluoromethyl-1,2-
dihydro-pyridine-3-carbonitrile

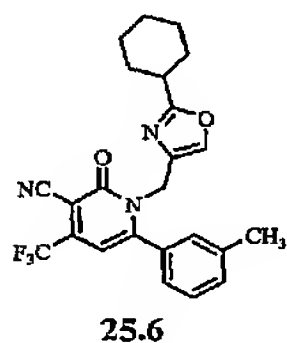
MS(ES⁺): 436.3 (M+H)

-262-



1-(2-Benzyl-oxazol-4-ylmethyl)-2-oxo-
6-*m*-tolyl-4-trifluoromethyl-1,2-
dihydro-pyridine-3-carbonitrile

$^1\text{H-NMR}$ (CDCl_3): δ 7.64 (s, 1H), 7.37-7.24 (m, 9H), 6.4 (s, 1H),
4.98 (s, 2H), 4.06 (s, 2H), 2.36 (s, 3H). MS(ES $^+$): 449.9 (M+H)



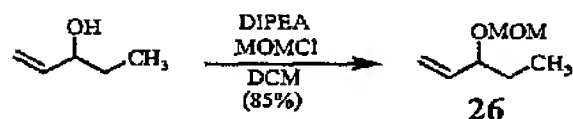
1-(2-Cyclohexyl-oxazol-4-ylmethyl)-2-
oxo-6-*m*-tolyl-4-trifluoromethyl-1,2-
dihydro-pyridine-3-carbonitrile

5

MS(ES $^+$): 442.0 (M+H)

EXAMPLE 26

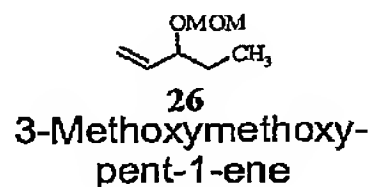
This example illustrates the preparation of compound **26**.



- Pent-1-en-3-ol (5.0 mL, 48.7 mmoles), N,N-
- 10** diisopropylethylamine (10.2 mL, 58.6 mmoles) and MOMCl (4.4 mL, 57.9 mmoles) were dissolved in 10 mL of anhydrous DCM within a sealed-tube, and this mixture was stirred at 50 °C for 20 hours. After this period the reaction mixture was combined with Et₂O and the resulting precipitate was removed by gravity filtration. The filtrate was carefully evaporated (-Et₂O and

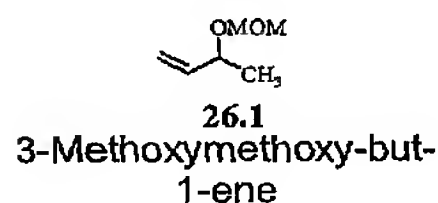
-263-

DCM) and the resulting amber liquid was fractionally distilled to yield 5.4g (85% yield) of **26** as a clear liquid. B.P. 126 °C @ 760mmHg



5 $^1\text{H-NMR}$ (CDCl_3): δ 5.72-5.61 (m, 1H), 5.23-5.16 (m, 2H), 4.71 (d, $J=6.8\text{Hz}$, 1H), 4.55 (d, $J=6.8\text{Hz}$, 1H), 3.91 (q, $J=7.1\text{Hz}$, 1H), 3.38 (s, 3H), 1.70-1.48 (m, 2H), 0.93 (t, $J=7.3\text{Hz}$, 3H).

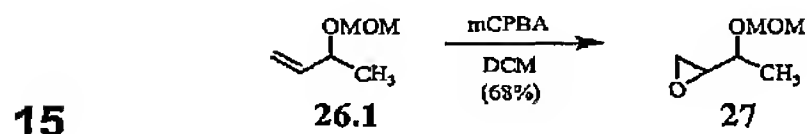
The following compounds were prepared in a manner similar to that described above.



10 $^1\text{H-NMR}$ (CDCl_3): δ 5.80-5.70 (m, 1H), 5.24-5.11 (m, 2H), 4.69 (d, $J=6.8\text{Hz}$, 1H), 4.58 (d, $J=6.8\text{Hz}$, 1H), 4.21-4.09 (m, 1H), 3.38 (s, 3H), 1.27 (d, $J=6.3\text{Hz}$, 3H).

EXAMPLE 27

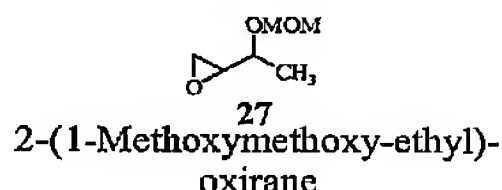
This example illustrates the preparation of compound **27**.



20 3-Methoxymethoxy-but-1-ene **26.1** (1.73 g, 14.9 mmol) was dissolved into 100 mL of DCM and to this stirring mixture at 0 °C was added 3-chloroperoxybenzoic acid (77% max, 7.4 g, ~30 mmol). This mixture was allowed to stir at room temperature for 20 hours. After this period the reaction mixture was combined with DCM and was washed with saturated $\text{Na}_2\text{S}_2\text{O}_3$ (2x20 mL) and 15 mL of saturated NaHCO_3 . After drying the resulting DCM

-264-

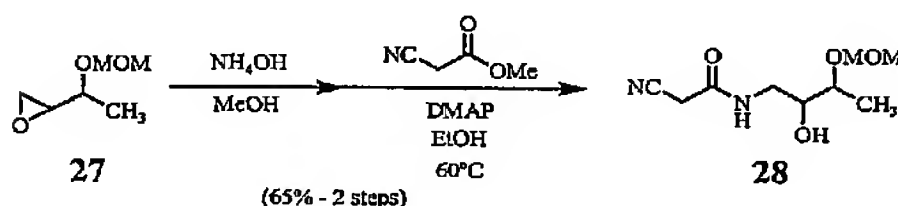
solution over anhydrous Na_2SO_4 the mixture was carefully evaporated *in vacuo* to yield crude product. The crude product was purified using flash silica chromatography (0-15% EtOAc/Hexane) to yield 1.34 g (68% yield) of **27** as yellowish liquid. Both ^1H -NMR and TLC analysis show **27** to be a 1:1 mixture of diastereomers.



^1H -NMR (CDCl_3): (diastereomers) δ 4.81 (d, $J=6.6\text{Hz}$, 1H), 4.72-4.67 (m, 2H), 4.64 (d, $J=6.6\text{Hz}$, 1H), 3.65-3.57 (m, 1H), 3.53-3.44 (m, 1H), 3.40 (s, 3H), 3.37 (s, 3H), 3.02-2.98 (m, 1H), 2.95-2.91 (m, 1H), 2.81-2.76 (m, 2H), 2.73-2.70 (m, 1H), 2.57-2.54 (m, 1H).

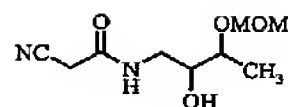
EXAMPLE 28

This example illustrates the preparation of compound **28**.



2-(1-Methoxymethoxy-ethyl)-oxirane **27** (1.89 g, 14.3 mmol) was combined with NH_4OH (28% NH_3 in water, 5 mL) and 1 mL of MeOH within a sealed-tube and this mixture was vigorously stirred at room temperature for 48 hours. After this period the reaction mixture was evaporate *in vacuo* ($-\text{NH}_3$ and H_2O) to yield crude product as an amber liquid. This product was combined with methyl cyanoacetate (3.0 mL, 34.0 mmol), DMAP (10 mg) and 50 mL of anhydrous EtOH. This mixture was stirred at 60 $^\circ\text{C}$ for 48 hours. After this period the reaction mixture was evaporated *in vacuo* and was purified using flash silica chromatography (0-100% EtOAc/Hexane) to yield 2.02 g (65% yield) of **28** as an amber residue. Both ^1H -NMR and TLC analysis show **28** to be a 1:1 mixture of diastereomers.

-265-



28

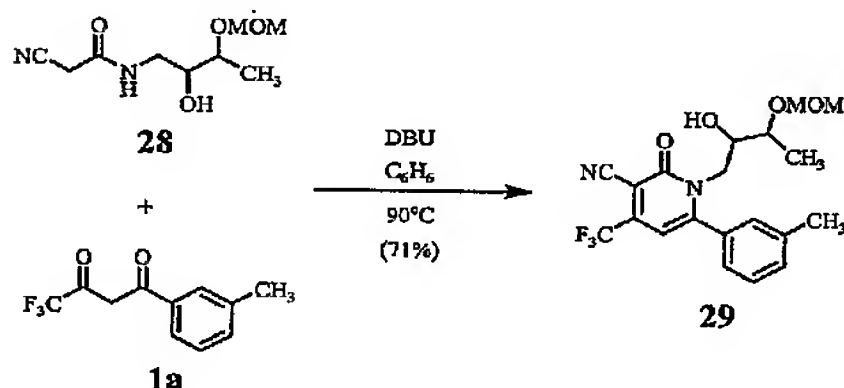
2-Cyano-N-(2-hydroxy-3-methoxymethoxy-butyl)-acetamide

$^1\text{H-NMR}$ (CDCl_3): (diastereomers) δ 6.78 & 6.64 (bs, 1H – both peaks), 4.77-4.65 (m, 2H), 3.84-3.54 (m, 3H), 3.45-3.36 (m, 6H), 3.32-3.14 (m, 2H), 1.13 (d, $J=6.3\text{Hz}$, 3H).

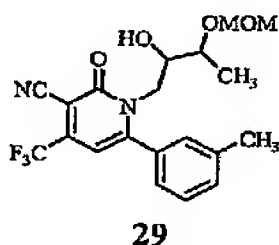
5

EXAMPLE 29

This example illustrates the preparation of compound **29**.



2-Cyano-N-(2-hydroxy-3-methoxymethoxy-butyl)-acetamide **28** (0.78 g, 3.6 mmoles) and 4,4,4-Trifluoro-1-m-tolyl-butane-1,3-dione **1a** (0.83 g, 3.6 mmoles) were dissolved in 10 mL of C_6H_6 and this mixture was stirred at 90 °C for 16 hours. After this period the reaction mixture was purified directly using flash silica chromatography (0-40% EtOAc/Hexane) to yield 1.06 g (71% yield) of **29** as a yellow liquid. $^1\text{H-NMR}$ analysis shows **29** to be a 1:1 mixture of diastereomers.



29

1-(2-Hydroxy-3-methoxymethoxy-butyl)-2-oxo-6-*m*-tolyl-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile

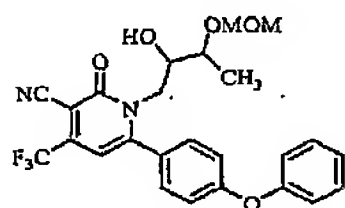
15

-266-

¹H-NMR (CDCl₃): (diastereomers) δ 7.44-7.32 (m, 4H), 7.21 (bs, 4H), 6.40 (bs, 2H), 4.58-4.45 (m, 4H), 4.28-4.09 (m, 4H), 3.90-3.82 (m, 1H), 3.81-3.73 (m, 1H), 3.71-3.63 (m, 1H), 3.57-3.49 (m, 1H), 3.22 (s, 3H), 3.10 (s, 3H), 2.43 (s, 6H), 1.14 (d, J=6.3Hz, 3H), 1.07 (d, J=6.6Hz, 3H).

5

The following compounds were prepared in a manner similar to that described above.



29.1

1-(2-Hydroxy-3-methoxymethoxy-butyl)-2-oxo-6-(4-phenoxy-phenyl)-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile

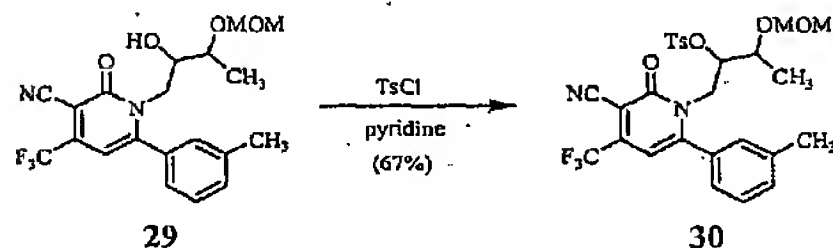
¹H-NMR (CDCl₃): (diastereomers) δ 7.45-7.33 (m, 8H), 7.24-7.19 (m, 2H), 7.11-7.02 (m, 8H), 6.36 (s, 1H), 6.35 (s, 1H), 4.62-4.51 (m, 4H), 4.30-4.15 (m, 4H), 3.96-3.82 (m, 2H), 3.75-3.66 (m, 1H), 3.62-3.54 (m, 1H), 3.26 (s, 3H), 3.19 (s, 3H), 1.15 (d, J=6.3Hz, 3H), 1.11 (d, J=6.3Hz, 3H).

10.

EXAMPLE 30

15

This example illustrates the preparation of compound 30.



1-(2-Hydroxy-3-methoxymethoxy-butyl)-2-oxo-6-m-tolyl-4-

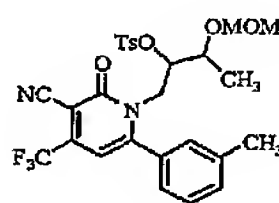
trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile 29 (0.36 g, 0.87 mmoles)

was combined with *p*-toluenesulfonyl chloride (0.33 g, 1.73 mmoles) in 2 mL

20 of pyridine and this mixture was stirred at room temperature for 16 hours.

-267-

After this period the mixture was evaporated and purified using flash silica chromatography (0-20% EtOAc/Hexane) to yield 0.33 g (67% yield) of **30** as a yellow residue. ¹H-NMR analysis shows **30** to be a 1:1 mixture of diastereomers.

**30**

Toluene-4-sulfonic acid 1-(3-cyano-2-oxo-6-*m*-tolyl-4-trifluoromethyl-2*H*-pyridin-1-ylmethyl)-2-methoxymethoxy-propyl ester

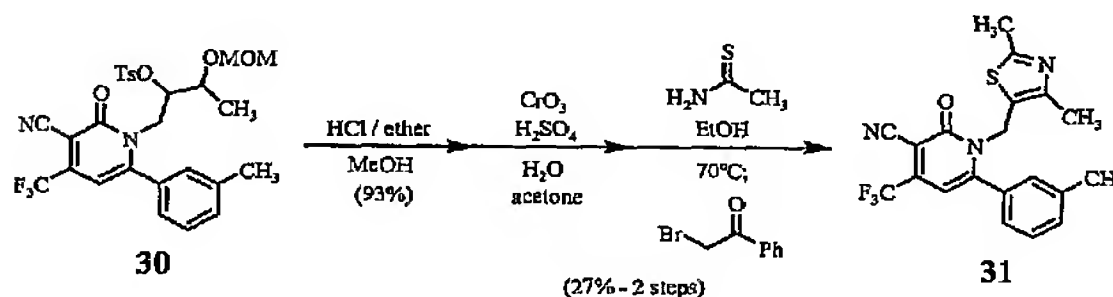
5

¹H-NMR (CDCl₃): (diastereomers) δ 7.68-7.61 (m, 4H), 7.46-7.28 (m, 4H), 6.33 (s, 1H), 6.33 (s, 1H), 5.06-5.00 (m, 1H), 4.88-4.82 (m, 1H), 4.52-4.45 (m, 2H), 4.38 (q, J=6.8Hz, 2H), 4.33-4.02 (m, 4H), 3.96-3.89 (m, 1H), 3.28 (s, 3H), 3.14 (s, 3H), 2.49 (s, 3H), 2.49 (s, 3H), 2.44 (s, 3H), 2.43 (s, 3H), 1.14 (d, J=6.8Hz, 3H), 0.85 (d, J=6.6Hz, 3H).

10

EXAMPLE 31

This example illustrates the preparation of compound **31**.



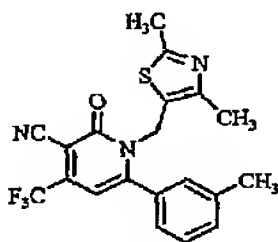
Toluene-4-sulfonic acid 1-(3-cyano-2-oxo-6-*m*-tolyl-4-

15 trifluoromethyl-2*H*-pyridin-1-ylmethyl)-2-methoxymethoxy-propyl ester **30** (0.28 g, 0.50 mmoles) was dissolved into 7 mL of anhydrous MeOH and to this solution was added HCl (2.0 M solution in diethyl ether, 1.0 mL) and this mixture was stirred at room temperature for 2 hours. After this period the reaction mixture was evaporated *in vacuo* and was purified using flash silica

20 chromatography (0-40% EtOAc/Hexane) to yield 0.24 g (93% yield) of **31** as a

-268-

yellow residue. $^1\text{H-NMR}$ analysis shows **31** to be a 1:1 mixture of diastereomers.

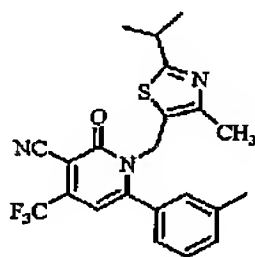
**31**

1-(2,4-Dimethyl-thiazol-5-ylmethyl)-2-oxo-6-*m*-tolyl-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile

5

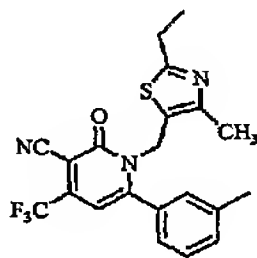
$^1\text{H-NMR}$ (CDCl_3): δ 7.47-7.38 (m, 2H), 7.13-7.06 (m, 2H), 6.37 (s, 1H), 5.28 (s, 2H), 2.58 (s, 3H), 2.43 (s, 3H). MS(ES⁺): 403.8 (M+H)

The following compounds were prepared in a manner similar to that described above.

**31.1**

1-(2-Isopropyl-4-methyl-thiazol-5-ylmethyl)-2-oxo-6-*m*-tolyl-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile

MS(ES⁺): 432.3 (M+H)

**31.2**

1-(2-Ethyl-4-methyl-thiazol-5-ylmethyl)-2-oxo-6-*m*-tolyl-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile

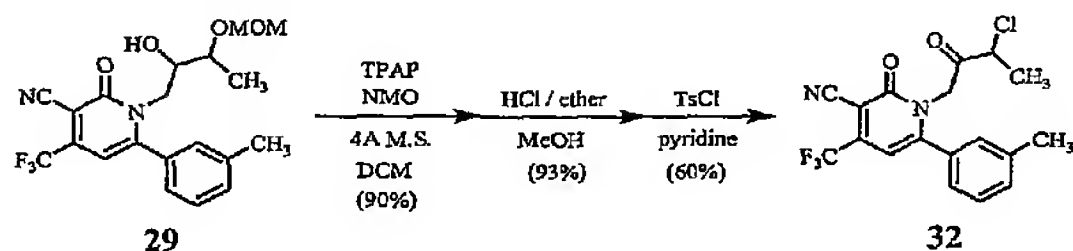
10

MS(ES⁺): 418.2 (M+H)

-269-

EXAMPLE 32

This example illustrates the preparation of compound **32**.



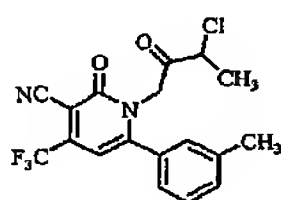
- 1-(2-Hydroxy-3-methoxymethoxy-butyl)-2-oxo-6-m-tolyl-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile **29** (0.21 g, 0.52 mmoles) was combined with N-methylmorpholine N-oxide (NMO, 92 mg, 0.79 mmoles) and 4Å molecular sieves (powder, 170 mg) in 5 mL of anhydrous DCM within a 7 mL reaction vial. The mixture was stirred at room temperature for 10 min. After this period tetrapropylammonium perruthenate (TPAP, 10mg, 0.028 mmoles) was added and the mixture was stirred at room temperature for an additional 3 hours. After this period the reaction mixture was purified directly using flash silica chromatography (0-40% EtOAc/Hexane) to yield 0.191 g (90% yield) of 1-(3-Methoxymethoxy-2-oxo-butyl)-2-oxo-6-m-tolyl-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile as a yellow residue.
- ¹H-NMR (CDCl₃): δ 7.42-7.35 (m, 2H), 7.14-7.07 (m, 2H), 6.45 (s, 1H), 5.04-4.91(m, 2H), 4.63-4.55 (m, 2H), 4.20 (q, J=6.8Hz, 1H), 3.22 (s, 3H), 2.40 (s, 3H), 1.31 (d, J=7.1Hz, 3H).

- 1-(3-Methoxymethoxy-2-oxo-butyl)-2-oxo-6-m-tolyl-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile (0.191 g, 0.47 mmoles) was dissolved into 25 mL of anhydrous MeOH and to this solution was added HCl (2.0 M solution in diethyl ether, 5.0 mL). The mixture was then stirred at room temperature for 2 hours. After this period the reaction mixture was evaporated *in vacuo* and was purified using flash silica chromatography (0-60% EtOAc/Hexane) to yield 0.16 g (93% yield) of 1-(3-Hydroxy-2-oxo-butyl)-2-oxo-6-m-tolyl-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile as a yellow residue. ¹H-NMR (CDCl₃): δ 7.42-7.35 (m, 2H), 7.14-7.08 (m, 2H), 6.50 (m, 1H), 5.06 (d,

-270-

J=17.2Hz, 1H), 4.92 (d, J=17.2Hz, 1H), 4.39-4.31 (m, 1H), 3.48 (bs, 1H), 2.40 (s, 3H), 1.28 (d, J=6.8Hz, 3H).

1-(3-Hydroxy-2-oxo-butyl)-2-oxo-6-*m*-tolyl-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile (98 mg, 0.27 mmoles) was combined with *p*-toluenesulfonyl chloride (0.1 g, 0.52 mmoles) in 2.0 mL of pyridine. The mixture was stirred at room temperature for 16 hours. After this period the reaction mixture was evaporated *in vacuo* and was purified using flash silica chromatography (0-20% EtOAc/Hexane) to yield 62 mg (60% yield) of **32** as a yellow residue.

**32**

10

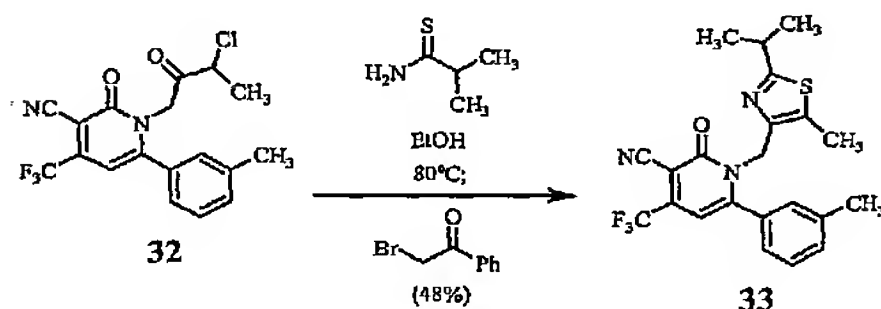
1-(3-Chloro-2-oxo-butyl)-2-oxo-6-*m*-tolyl-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile

¹H-NMR (CDCl₃): δ 7.44-7.35 (m, 2H), 7.16-7.11 (m, 2H), 6.49 (s, 1H), 5.02-4.92 (m, 2H), 4.55 (q, J=6.8Hz, 1H), 2.42 (s, 3H), 1.65 (d, J=6.8Hz, 3H).

EXAMPLE 33

15

This example illustrates the preparation of compound **33**.

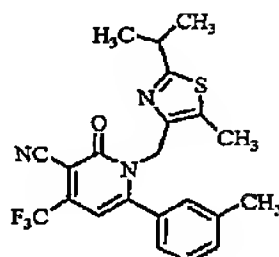


20

1-(3-Chloro-2-oxo-butyl)-2-oxo-6-*m*-tolyl-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile **32** (41 mg, 0.11 mmoles) was combined with thioisobutyramide (22 mg, 0.22 mmoles) in 1.0 mL of anhydrous EtOH within a 7 mL reaction vial. This mixture was stirred at 80 °C for 16 hours. After this

-271-

period 2-bromoacetophenone (33 mg, 0.17 mmoles) was added and the reaction was stirred at 80 °C for an additional 3 hours. After this period the reaction mixture was evaporated *in vacuo* and was purified using flash silica chromatography (0-40% EtOAc/Hexane) and normal-phase HPLC (YMC-Pack SIL, 250x50 mm I.D., S-5 μ M: 4-20% EtOAc/Hexane over 30 minutes) to yield 22 mg (48% yield) of **33** as a yellow residue.

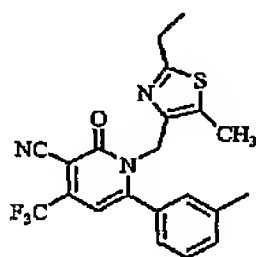
**33**

1-(2-Isopropyl-5-methyl-thiazol-4-ylmethyl)-2-oxo-6-*m*-tolyl-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile

¹H-NMR (CDCl₃): δ 7.53-7.29 (4H), 6.40 (s, 1H), 5.03 (s, 2H), 3.13 (m, J=6.6Hz, 1H), 2.40 (s, 3H), 2.38 (s, 3H), 1.32 (d, J=6.8Hz, 6H).

10 MS(ES⁺): 432.1 (M+H)

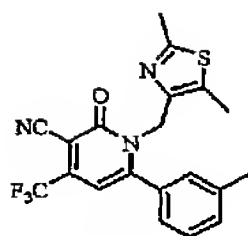
The following compounds were prepared in a manner similar to that described above.

**33.1**

1-(2-Ethyl-5-methyl-thiazol-4-ylmethyl)-2-oxo-6-*m*-tolyl-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile

MS(ES⁺): 417.9 (M+H)

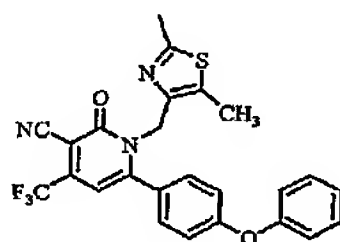
-272-



33.2

1-(2,5-Dimethyl-thiazol-4-ylmethyl)-2-oxo-6-*m*-tolyl-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile

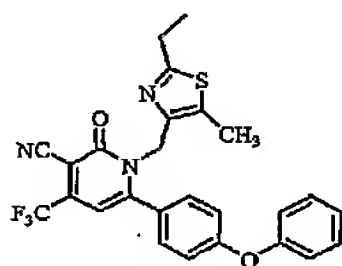
MS(ES⁺): 404.2 (M+H)



33.3

1-(2,5-Dimethyl-thiazol-4-ylmethyl)-2-oxo-6-(4-phenoxy-phenyl)-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile

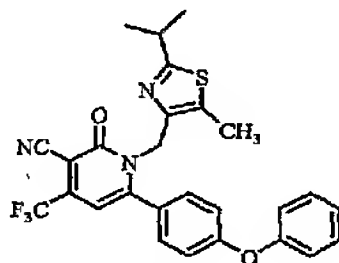
MS(ES⁺): 482.1 (M+H)



33.4

1-(2-Ethyl-5-methyl-thiazol-4-ylmethyl)-2-oxo-6-(4-phenoxy-phenyl)-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile

MS(ES⁺): 496.2 (M+H)

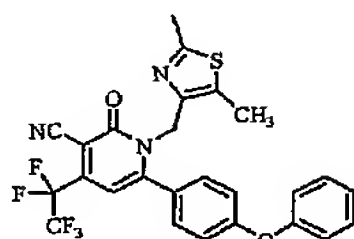


33.5

1-(2-Isopropyl-5-methyl-thiazol-4-ylmethyl)-2-oxo-6-(4-phenoxy-phenyl)-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile

-273-

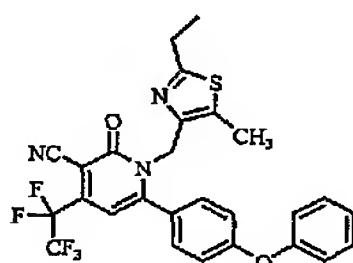
MS(ES⁺): 510.1 (M+H)



33.6

1-(2,5-Dimethyl-thiazol-4-ylmethyl)-2-oxo-4-pentafluoroethyl-6-(4-phenoxy-phenyl)-1,2-dihydro-pyridine-3-carbonitrile

MS(ES⁺): 532.0 (M+H)

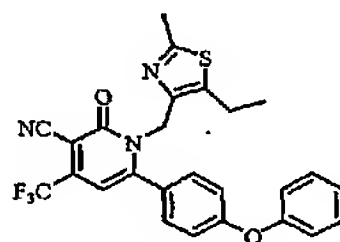


33.7

1-(2-Ethyl-5-methyl-thiazol-4-ylmethyl)-2-oxo-4-pentafluoroethyl-6-(4-phenoxy-phenyl)-1,2-dihydro-pyridine-3-carbonitrile

5

MS(ES⁺): 546.4 (M+H)

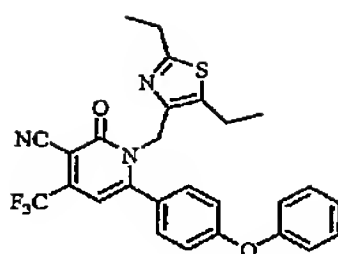


33.8

1-(5-Ethyl-2-methyl-thiazol-4-ylmethyl)-2-oxo-6-(4-phenoxy-phenyl)-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile

MS(ES⁺): 496.1 (M+H)

-274-



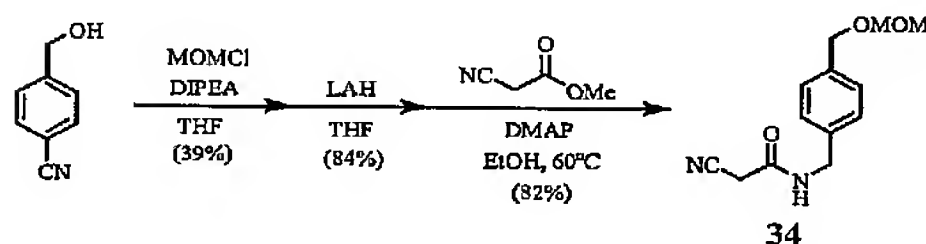
33.9

1-(2,5-Diethyl-thiazol-4-ylmethyl)-2-oxo-6-(4-phenoxy-phenyl)-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile

MS(ES⁺): 510.1 (M+H)

EXAMPLE 34

This example illustrates the preparation of compound 34.



5

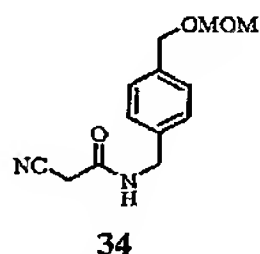
4-Hydroxymethyl-benzonitrile (3.1 g, 23.3 mmoles) was combined with N,N-diisopropylethylamine (4.9 mL, 28 mmoles) in 100 mL of anhydrous THF. To this solution was added MOMCl (3.5 mL, 46.1 mmoles) and the mixture was stirred at room temperature for 16 hours. After this period a solution of NH₄OH/H₂O (1:1, 20 mL) was added (-MOMCl) and the solution was stirred for 15 minutes. After this period the reaction mixture was evaporated *in vacuo* (-THF) and the resulting mixture was extracted with DCM (3x30 mL). The combined DCM layer was dried over anhydrous Na₂SO₄, evaporated *in vacuo*, and the resulting crude product was purified using flash silica chromatography (0-20% EtOAc/Hexane) to yield 1.6 g (39% yield) of 4-Methoxymethoxymethylbenzonitrile as a colorless liquid.

4-Methoxymethoxymethylbenzonitrile (3.7 g, 20.9 mmoles) was dissolved into 100 mL of anhydrous THF and was placed under dry N₂ atmosphere. To this solution at 0 °C was added lithium aluminum hydride (LAH, 1.6 g, 42.2 mmoles, bubbling occurs) and this mixture (sealed under

20

-275-

- N₂) was gently stirred at 75 °C for 12 hours. After this period the mixture was cooled down and placed into an ice bath under a dry N₂ atmosphere. To the vigorously stirring mixture at 0 °C was slowly and carefully sequentially added water (2 mL), 15% NaOH (2 mL) and water (4 mL). The resulting
- 5 heterogenous mixture was vacuum filtered and the filtrate was evaporated *in vacuo* to yield 3.2 g (17.7 mmoles, 84% yield) of crude amine as a yellowish residue. The crude amine was combined with methyl cyanoacetate (3.1 mL, 35.1 mmoles) and DMAP (10 mg) in 50 mL of anhydrous EtOH. The mixture was then stirred at 60 °C for 16 hours. After this period the reaction mixture
- 10 was evaporated *in vacuo* and was purified using flash silica chromatography (0-60% EtOAc/Hexane) to 3.6 g (82% yield) of **34** as a white powder.

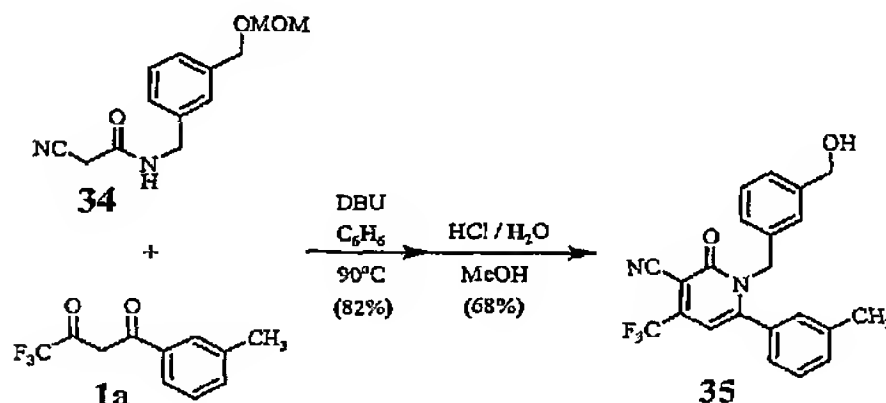


2-Cyano-N-(4-methoxymethoxymethylbenzyl)-acetamide

- ¹H-NMR (CDCl₃): δ 7.36 (d, J=8.1Hz, 2H), 7.28 (d, J=8.3Hz, 2H), 6.34 (bs, 1H), 4.71 (s, 2H), 4.59 (s, 2H), 4.48 (d, J=5.6Hz, 2H),
- 15 3.41 (s, 3H), 3.40 (s, 2H).

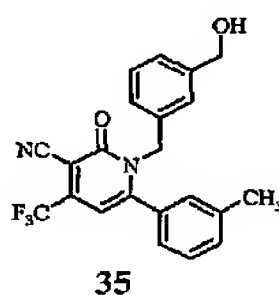
EXAMPLE 35

This example illustrates the preparation of compound **35**.



-276-

- 2-Cyano-N-(4-methoxymethoxymethyl-benzyl)-acetamide (0.84 g, 3.4 mmol) was combined with **1a** (0.78g, 3.4 mmol), DBU (0.25 mL, 1.7 mmol) and 5 mL of C₆H₆ within a 7 mL reaction vial. The mixture was stirred at 90 °C for 16 hours. After this period the reaction mixture was
- 5 purified directly using flash silica chromatography (0-20% EtOAc/Hexane) to yield 1.23 g (82% yield) of **35** as a yellow residue. ¹H-NMR (CDCl₃): δ 7.37-7.31 (m, 2H), 7.26-7.19 (m, 2H), 7.03-6.97 (m, 1H), 6.93 (bs, 1H), 6.89 (bs, 1H), 6.86-6.81 (m, 1H), 6.39 (s, 1H), 5.24 (bs, 2H), 4.67 (s, 2H), 4.50 (s, 2H), 3.39 (s, 3H), 2.33 (s, 3H). MS(ES⁺): 443.2 (M+H)
- 10 1-(3-Methoxymethoxymethyl-benzyl)-2-oxo-6-*m*-tolyl-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile (0.65 g, 1.47 mmol) was dissolved into 10 mL of MeOH and to this was added 12N HCl (100 μL). This mixture was then stirred at room temperature for 3 hours. After this period the reaction mixture was evaporated *in vacuo* and was purified using flash silica chromatography
- 15 (0-40% EtOAc/Hexane) to yield 0.40 g (68% yield) of **31** as a yellow residue.

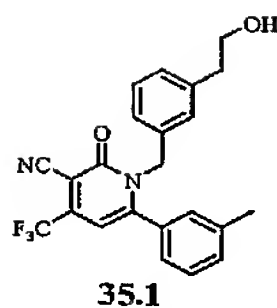


1-(3-Hydroxymethyl-benzyl)-2-oxo-6-*m*-tolyl-4-trifluoromethyl-
1,2-dihydro-pyridine-3-carbonitrile

¹H-NMR (CDCl₃): δ 7.36-7.32 (m, 2H), 7.26-7.19 (m, 2H), 7.02-6.97 (m, 1H), 6.92 (d, J=10Hz, 2H), 6.82 (d, J=6.8Hz, 1H), 6.39 (s, 1H), 5.24 (bs, 2H), 4.62 (s, 2H), 2.34 (s, 3H). MS(ES⁺): 398.8 (M+H)

- 20 The following compounds were prepared in a manner similar to that described above.

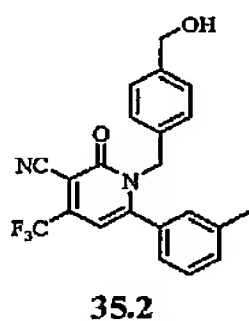
-277-



1-[3-(2-Hydroxy-ethyl)-benzyl]-2-oxo-
6-*m*-tolyl-4-trifluoromethyl-1,2-
dihydro-pyridine-3-carbonitrile

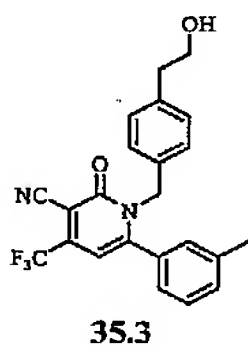
¹H-NMR (CDCl₃): δ 7.36-7.33 (m, 2H), 7.11 (d, J=8.1Hz, 2H),
7.04-7.00 (m, 1H), 6.95 (s, 1H), 6.87 (d, J=8.1Hz, 2H), 6.39 (s, 1H),
5.22 (bs, 2H), 3.82 (q, J=5.8Hz, 2H), 2.82 (t, J=6.8Hz, 2H), 2.34 (s,
3H).

5



1-(4-Hydroxymethyl-benzyl)-2-oxo-
6-*m*-tolyl-4-trifluoromethyl-1,2-
dihydro-pyridine-3-carbonitrile

MS(ES⁺): 398.9 (M+H)



1-[4-(2-Hydroxy-ethyl)-benzyl]-2-oxo-6-
m-tolyl-4-trifluoromethyl-1,2-dihydro-
pyridine-3-carbonitrile

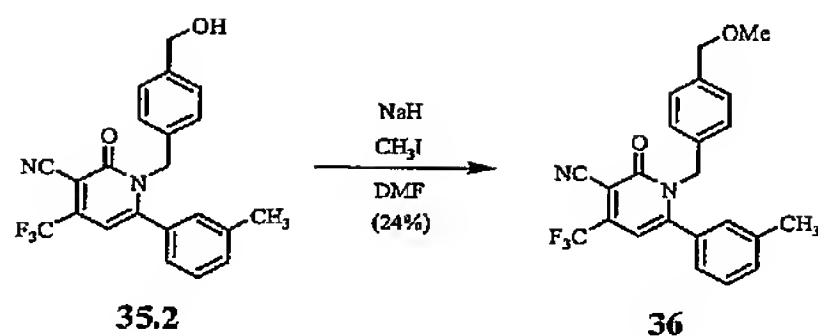
MS(ES⁺): 413.3 (M+H)

10

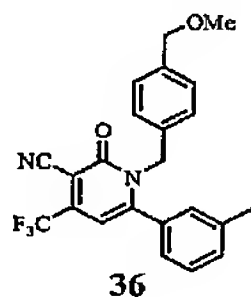
EXAMPLE 36

This example illustrates the preparation of compound **36**.

-278-



- 1-(4-Hydroxymethyl-benzyl)-2-oxo-6-*m*-tolyl-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile **35.2** (41 mg, 0.10 mmoles) was dissolved into 1.0 mL of anhydrous N,N-dimethyl-formamide. To this solution was then added sodium hydride (60% dispersion in mineral oil, 5 mg, 0.125 mmoles) and the mixture was stirred (bubbling occurs) for 5 min. After this period iodomethane (15 μ L, 0.24 mmoles) was added and the mixture was stirred at room temperature for 16 hours. After this period the reaction mixture was combined with 20 mL of water and was extracted with EtOAc (4x15 mL). The combined organic layer was washed with water (4x15 mL), 15 mL of brine, and was dried over Na₂SO₄. The EtOAc solution was evaporated *in vacuo* and purified using flash silica chromatography (0-20% EtOAc/Hexane) to yield 10 mg (24%) of **36** as a yellow residue.

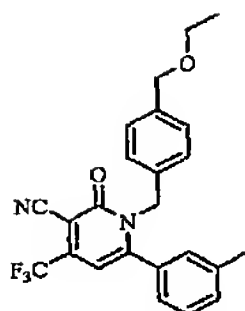


1-(4-Methoxymethyl-benzyl)-2-oxo-6-*m*-tolyl-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile

- ¹H-NMR (CDCl₃): δ 7.36-7.32 (m, 2H), 7.21 (d, J=7.8Hz, 2H), 7.02-6.96 (m, 1H), 6.93 (bs, 1H), 6.89 (d, J=7.6Hz, 2H), 6.38 (s, 1H), 5.23 (bs, 2H), 4.41 (s, 3H), 3.37 (s, 3H), 2.33 (s, 3H). MS(ES⁺): 413.3 (M+H)

The following compounds were prepared in a manner similar to that described above.

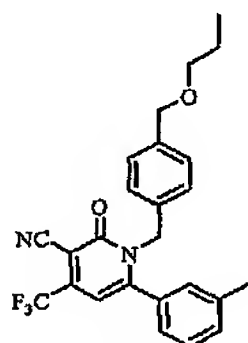
-279-



36.1

1-(4-Ethoxymethyl-benzyl)-2-oxo-
6-*m*-tolyl-4-trifluoromethyl-1,2-
dihydro-pyridine-3-carbonitrile

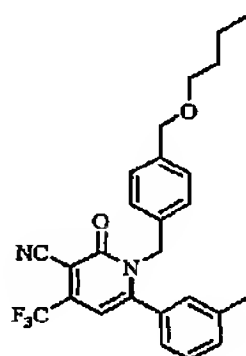
MS(ES⁺): 427.3 (M+H)



36.2

2-Oxo-1-(4-propoxymethyl-benzyl)-
6-*m*-tolyl-4-trifluoromethyl-1,2-
dihydro-pyridine-3-carbonitrile

MS(ES⁺): 441.2 (M+H)

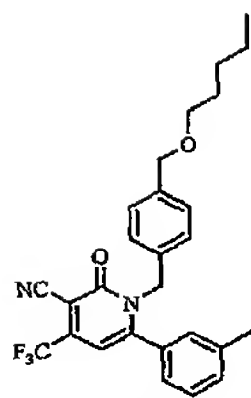


36.3

1-(4-Butoxymethyl-benzyl)-2-oxo-6-*m*-tolyl-4-trifluoromethyl-
1,2-dihydro-pyridine-3-carbonitrile

MS(ES⁺): 455.2 (M+H)

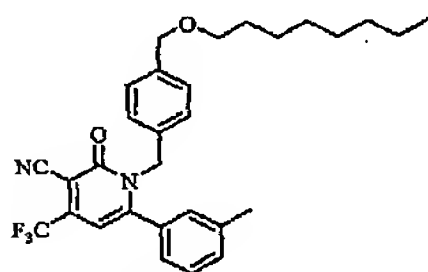
-280-



36.4

2-Oxo-1-(4-pentyloxymethyl-benzyl)-
6-*m*-tolyl-4-trifluoromethyl-1,2-
dihydro-pyridine-3-carbonitrile

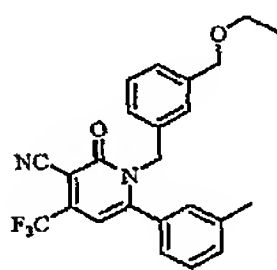
MS(ES⁺): 469.2 (M+H)



36.5

1-(4-Octyloxymethyl-benzyl)-2-oxo-
6-*m*-tolyl-4-trifluoromethyl-1,2-
dihydro-pyridine-3-carbonitrile

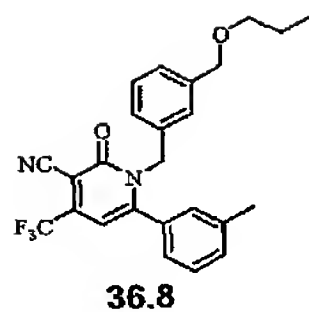
MS(ES⁺): 511.1 (M+H)^δ



36.7

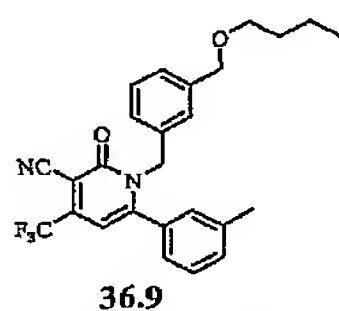
1-(3-Ethoxymethyl-benzyl)-2-oxo-
6-*m*-tolyl-4-trifluoromethyl-1,2-
dihydro-pyridine-3-carbonitrile

MS(ES⁺): 427.2 (M+H)

-281-

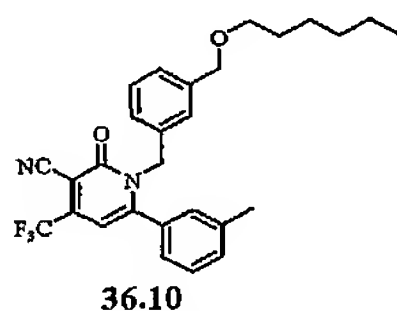
2-Oxo-1-(3-propoxymethyl-benzyl)-
6-*m*-tolyl-4-trifluoromethyl-1,2-
dihydro-pyridine-3-carbonitrile

MS(ES⁺): 441.1 (M+H)



1-(3-Butoxymethyl-benzyl)-2-oxo-
6-*m*-tolyl-4-trifluoromethyl-1,2-
dihydro-pyridine-3-carbonitrile

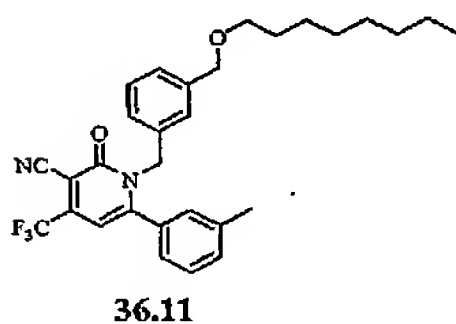
MS(ES⁺): 455.2 (M+H)



1-(3-Hexyloxymethyl-benzyl)-6-(3-methyl-
1-methylene-but-2-enyl)-2-oxo-4-
trifluoromethyl-1,2-dihydro-pyridine-3-
carbonitrile

5

MS(ES⁺): 483.1 (M+H)

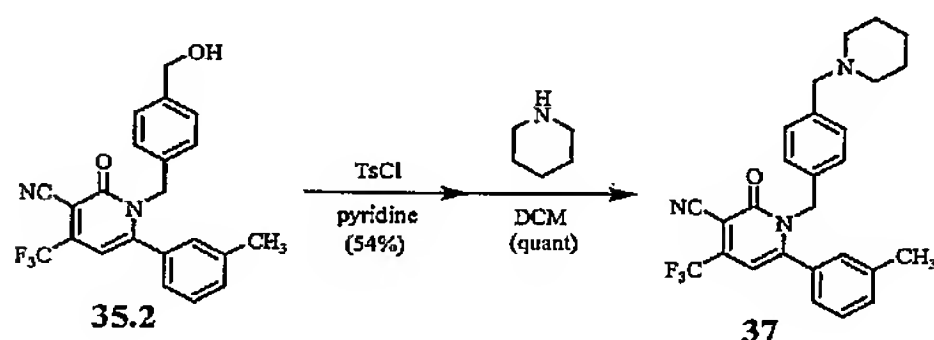


1-(3-Octyloxymethyl-benzyl)-2-oxo-
6-*m*-tolyl-4-trifluoromethyl-1,2-
dihydro-pyridine-3-carbonitrile

-282-

MS(ES⁺): 511.0 (M+H)**EXAMPLE 37**

This example illustrates the preparation of compound **37**.

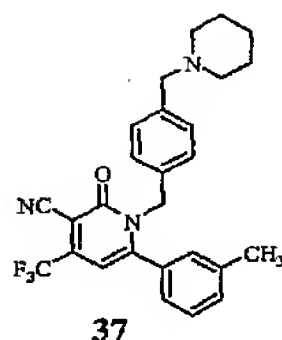


- 5** 1-(3-Hydroxymethyl-benzyl)-2-oxo-6-m-tolyl-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile **35.2** (29 mg, 0.073 mmoles) was combined with *p*-toluenesulfonyl chloride (25 mg, 0.13 mmoles) in 1.0 mL of pyridine and this mixture was stirred at room temperature for 16 hours. After this period the reaction mixture was evaporated *in vacuo* and was purified using
- 10** flash silica chromatography (0-20% EtOAc/Hexane) to yield 16mg (54% yield) of **37a** as a yellow residue. ¹H-NMR (CDCl₃): δ 7.33 (d, J=5.3Hz, 2H), 7.20 (br d, J=7.6Hz, 2H), 7.03-6.99 (m, 1H), 6.91 (s, 1H), 6.85 (d, J=7.8Hz, 2H), 6.38 (br s, 1H), 5.22 (s, 2H), 3.45 (br s, 2H), 2.36 (br s, 4H), 2.32 (s, 3H), 1.57 (br s, 4H), 1.43 (br s, 2H).

15

- 1-(4-Chloromethyl-benzyl)-2-oxo-6-m-tolyl-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile **37a** (8 mg, 0.019 mmoles) was combined with 1.0 mL of DCM and piperidine (0.1 mL, 1.0 mmoles) within a 7 mL reaction vial. The mixture was stirred at room temperature for 2 hours. After this
- 20** period the reaction mixture was purified directly using flash silica chromatography (0-10% MeOH/DCM) to yield 9 mg (quantitative yield) of **37** as a yellow residue.

-283-

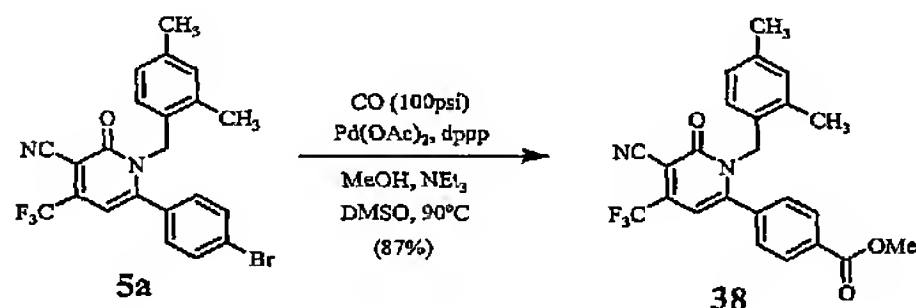


2-Oxo-1-(4-piperidin-1-ylmethyl-benzyl)-6-*m*-tolyl-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile

$^1\text{H-NMR}$ (CDCl_3): δ 7.33 (d, $J=5.1\text{Hz}$, 2H), 7.20 (bd, $J=7.3\text{Hz}$, 2H), 7.03-6.98 (m, 1H), 6.91 (m, 1H), 6.85 (d, $J=7.8\text{Hz}$, 2H), 5.22 (bs, 2H), 3.45 (bs, 2H), 2.45-2.28 (m, 4H), 2.32 (s, 3H), 1.63-1.52 (m, 4H), 1.48-1.38 (m, 2H). MS(ES $^+$): 466.2 (M+H)

EXAMPLE 38

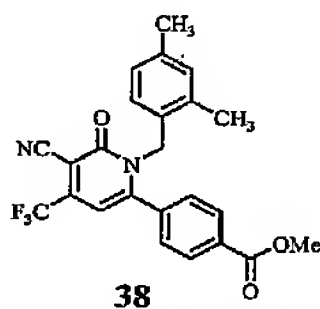
This example illustrates the preparation of compound **38**.



Within a Parr high-pressure apparatus were combined 6-(4-Bromo-phenyl)-1-(2,4-dimethyl-benzyl)-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile **5a** (0.51 g, 1.11 mmoles), $\text{Pd}(\text{OAc})_2$ (15 mg, 0.067 mmoles), and 1,3-bis(diphenylphosphino)propane (30 mg, 0.073 mmoles). This mixture was dissolved into 15 mL of anhydrous MeOH, 5 mL of anhydrous DMSO and NEt_3 (0.6 mL, 4.3 mmoles), and was pressured to 100 psi with CO. The pressured and stirring reaction mixture was then heated to 90 °C for 48 hours. After this period the reaction mixture was cooled to ambient temperature, depressurized, and was combined with 100 mL of water. The aqueous mixture was extracted with EtOAc (4x25 mL) and the combined EtOAc layer was washed with water (4x25 mL) and brine. After

-284-

drying over anhydrous Na_2SO_4 the crude product was purified using flash silica chromatography (0-30% EtOAc/Hexane) to yield 0.43 g (87% yield) of **38** as a yellow solid.

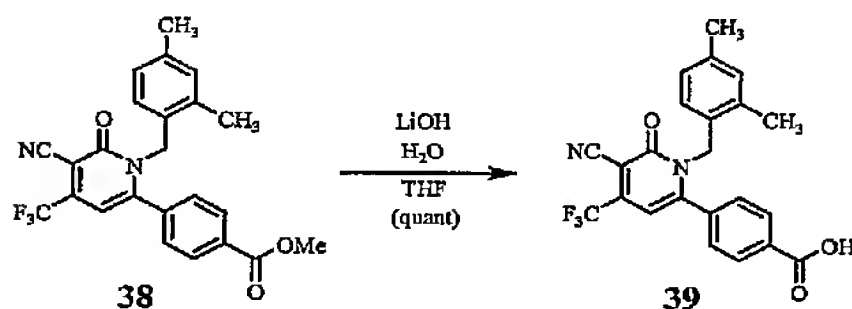


38
4-[5-Cyano-1-(2,4-dimethyl-benzyl)-6-oxo-4-trifluoromethyl-1,6-dihydro-pyridin-2-yl]-benzoic acid methyl ester

- 5 $^1\text{H-NMR}$ (CDCl_3): δ 8.03 (d, $J=8.3\text{Hz}$, 2H), 7.23 (d, $J=8.3\text{Hz}$, 2H), 6.95 (bd, $J=7.8\text{Hz}$, 1H), 6.89 (bs, 1H), 6.58 (d, $J=7.8\text{Hz}$, 1H), 6.42 (s, 1H), 5.09 (s, 2H), 3.95 (s, 3H), 2.28 (s, 3H), 1.88 (s, 3H).

EXAMPLE 39

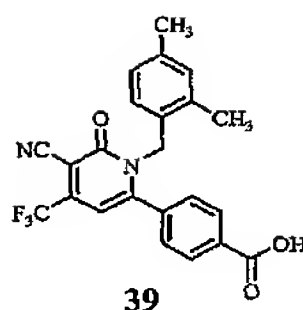
This example illustrates the preparation of compound **39**.



10

- 4-[5-Cyano-1-(2,4-dimethyl-benzyl)-6-oxo-4-trifluoromethyl-1,6-dihydro-pyridin-2-yl]-benzoic acid methyl ester **38** (0.105 g, 0.24 mmoles) was combined with LiOH (monohydrate, 22 mg, 0.52 mmoles) in 5 mL of THF and 1 mL of water. The mixture was stirred at room temperature for 90 minutes.
- 15 After this period the reaction mixture was concentrated *in vacuo* (-THF) and the resulting aqueous mixture was combined with 10 mL of 1N HCl and salt (enough to affect saturation after mixing). The acidic aqueous layer was extracted with Et_2O (3x20 mL) and the combined organic layer was washed with brine. The Et_2O layer was dried over anhydrous Na_2SO_4 and evaporated
- 20 *in vacuo* to yield 0.102 g (quantitative yield) as a yellowish solid.

-285-



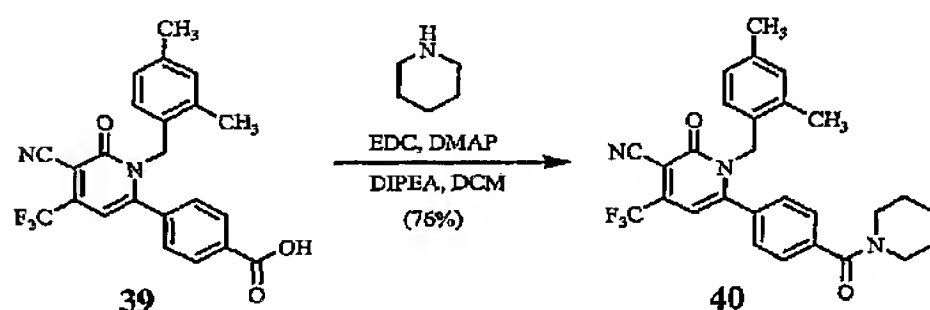
4-[5-Cyano-1-(2,4-dimethyl-benzyl)-6-oxo-4-trifluoromethyl-1,6-dihydro-pyridin-2-yl]-benzoic acid

$^1\text{H-NMR}$ (CDCl_3): δ 8.09 (d, $J=8.1\text{Hz}$, 2H), 7.29-7.25 (m, 2H), 6.95 (d, $J=7.8\text{Hz}$, 1H), 6.90 (s, 1H), 6.59 (d, $J=7.8\text{Hz}$, 1H), 6.43 (s, 1H), 5.10 (s, 2H), 2.29 (s, 3H), 1.89 (s, 3H). $\text{MS(ES}^+)$: 427.2 (M^+H)

5

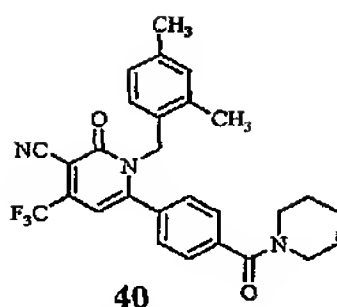
EXAMPLE 40

This example illustrates the preparation of compound **40**.



4-[5-Cyano-1-(2,4-dimethyl-benzyl)-6-oxo-4-trifluoromethyl-1,6-dihydro-pyridin-2-yl]-benzoic acid **39** (48 mg, 0.11 mmoles) was combined with 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride (EDC, 54 mg, 0.28 mmoles), 4-dimethylaminopyridine (DMAP, 2 mg, 0.016 mmoles) in 5 mL of anhydrous DCM. To this mixture was added diisopropylethylamine (DIPEA, 50 μL , 0.29 mmoles) and piperidine (28 μL , 0.28 mmoles). This mixture was then stirred at room temperature for 16 hours. After this period the reaction mixture was purified directly using flash silica chromatography (0-60% EtOAc/Hexane) to yield 41 mg (76% yield) of **40** as a yellow residue.

-286-

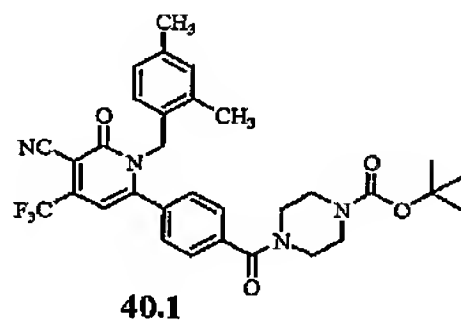


40
1-(2,4-Dimethyl-benzyl)-2-oxo-6-[4-(piperidine-1-carbonyl)-phenyl]-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile

5

$^1\text{H-NMR}$ (CDCl_3): δ 7.39 (d, $J=8.1\text{Hz}$, 2H), 7.19 (d, $J=8.1\text{Hz}$, 2H), 6.94 (bd, $J=8.1\text{Hz}$, 1H), 6.88 (bs, 1H), 6.59 (d, $J=7.8\text{Hz}$, 1H), 6.42 (s, 1H), 5.11 (s, 2H), 3.75-3.66 (m, 2H), 3.34-3.24 (m, 2H), 2.28 (s, 3H), 1.93 (s, 3H), 1.75-1.63 (m, 4H), 1.56-1.48 (m, 2H). $\text{MS(ES}^+)$: 494.3 (M+H)

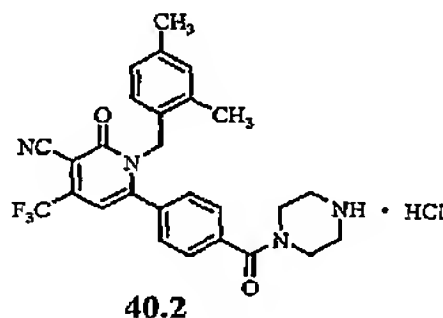
The following compounds were prepared in a manner similar to that described above.



40.1
4-{4-[5-Cyano-1-(2,4-dimethyl-benzyl)-6-oxo-4-trifluoromethyl-1,6-dihydro-pyridin-2-yl]-benzoyl}-piperazine-1-carboxylic acid *tert*-butyl ester

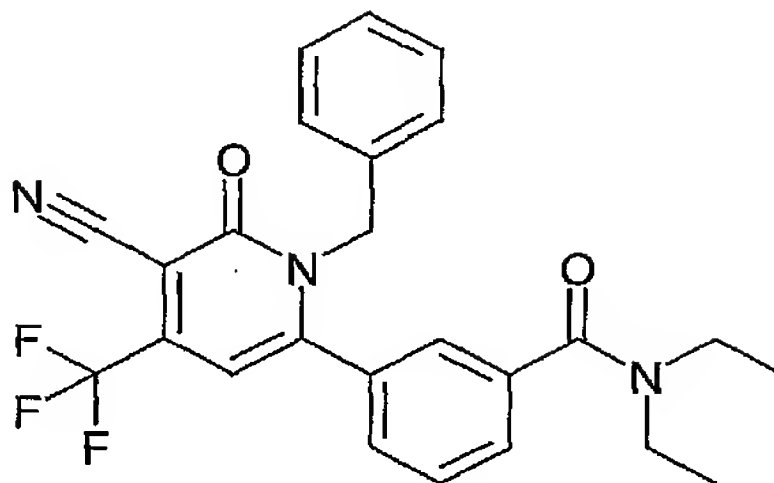
10

$\text{MS(ES}^+)$: 595.4 (M+H)



40.2
1-(2,4-Dimethyl-benzyl)-2-oxo-6-[4-(piperazine-1-carbonyl)-phenyl]-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile hydrochloride

-287-

MS(ES⁺): 495.2 (M+H)

40.3

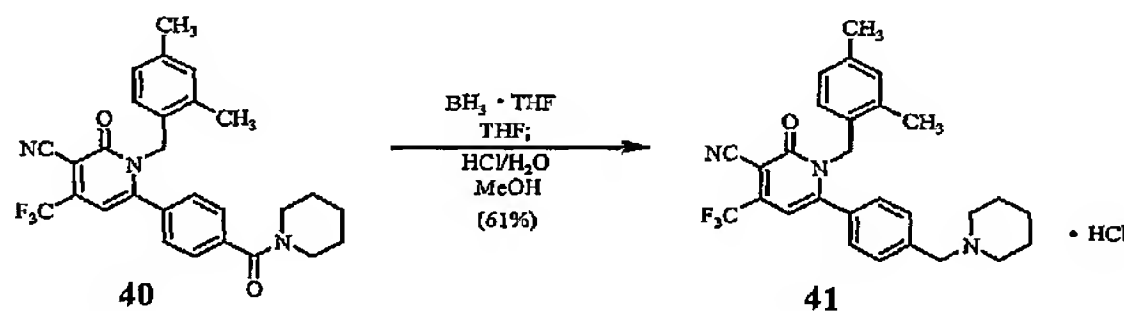
5 3-(1-Benzyl-5-cyano-6-oxo-4-trifluoromethyl-1,6-dihydro-pyridin-2-yl)-N,N-diethyl-benzamide

¹H-NMR (CDCl₃): δ7.54 (m, 1 H), 7.48 (m, 1 H), 7.23 (m, 5 H), 6.89 (m, 2 H), 6.4 (s, 1 H), 5.28 (s, 2 H), 3.52 (br, 2 H), 3.13 (br, 2 H), 1.20 (br, 3 H), 1.06 (br, 3 H).

10

EXAMPLE 41

This example illustrates the preparation of compound 41.



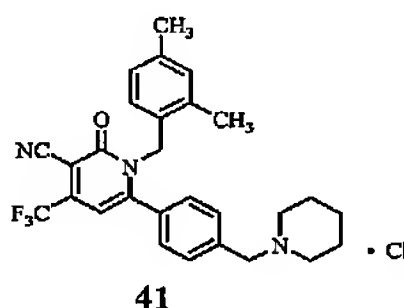
1-(2,4-Dimethyl-benzyl)-2-oxo-6-[4-(piperidine-1-carbonyl)-phenyl]-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile **40** (20 mg, 0.041

15 mmoles) was dissolved into 2.0 mL of anhydrous THF within a 7 mL reaction vial. To this stirring mixture at room temperature was added diborane-THF (160 μL, 0.16 mmoles) and the mixture was stirred at room temperature for 16 hours. After this period the reaction was quenched by adding 3 mL of 25% NH₄Cl. This aqueous mixture was stirred for 30 min. After this period the

20 resulting mixture was extracted with Et₂O (3x10 mL) and the resulting organic layer was washed with brine and dried over Na₂SO₄. The ether layer was evaporated *in vacuo* and the resulting crude product was purified using flash

-288-

silica chromatography (0-5% MeOH/DCM w/0.1% NEt₃) to yield the free base. The free base was combined with 2N HCl/MeOH, evaporated, dissolved into deionized water and lyophilized to yield 12 mg (61% yield) of **41** as a white powder.

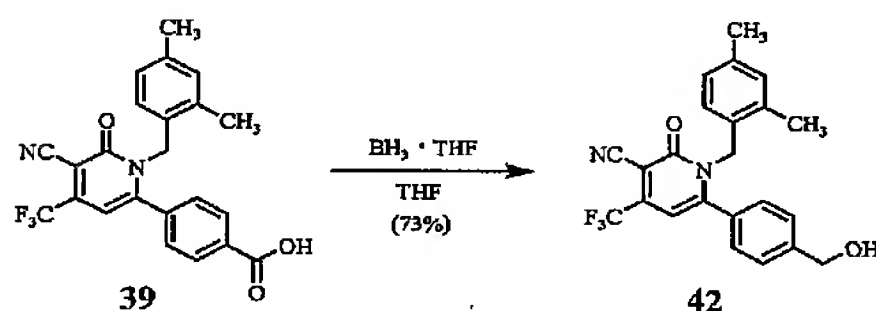


5 1-(2,4-Dimethyl-benzyl)-2-oxo-6-(4-piperidin-1-ylmethyl-phenyl)-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile hydrochloride

¹H-NMR (D₂O – free base): δ 7.31 (d, J=8.1Hz, 2H), 7.21 (d, J=8.1Hz, 2H), 6.86 (d, J=8.3Hz, 1H), 6.82 (s, 1H), 6.51 (d, J=7.3Hz, 1H), 5.09 (s, 2H), 4.14 (s, 2H), 3.27-3.17 (m, 2H), 2.84-2.70 (m, 2H), 2.10 (s, 3H), 1.87-1.24 (m, 6H), 2.10 (s, 3H), 1.75 (s, 3H). MS(ES⁺):
10 480.2 (M+H)

EXAMPLE 42

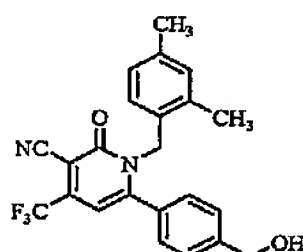
This example illustrates the preparation of compound **42**.



15 4-[5-Cyano-1-(2,4-dimethyl-benzyl)-6-oxo-4-trifluoromethyl-1,6-dihydro-pyridin-2-yl]-benzoic acid **39** (27 mg, 0.063 mmoles) was dissolved into 2.0 mL of anhydrous THF within a 7 mL reaction vial. To this stirring solution at 0 °C was added diborane-THF (0.11 mL, 0.11 mmoles). The reaction was then allowed to warm to room temperature and was stirred for 16 hours. After this period the reaction was quenched by adding 3 mL of 25%

-289-

NH₄Cl, and this mixture was stirred for 30 min. The resulting aqueous mixture was evaporated *in vacuo* (-THF) and extracted with Et₂O (3x10 mL). The combined ether layer was washed with saturated NaHCO₃, dried over Na₂SO₄ and was evaporated *in vacuo* to yield the crude residue. The crude residue
 5 was purified using flash silica chromatography (0-60% EtOAc/Hexane) to yield 19 mg (73% yield) of **42** as a white solid.

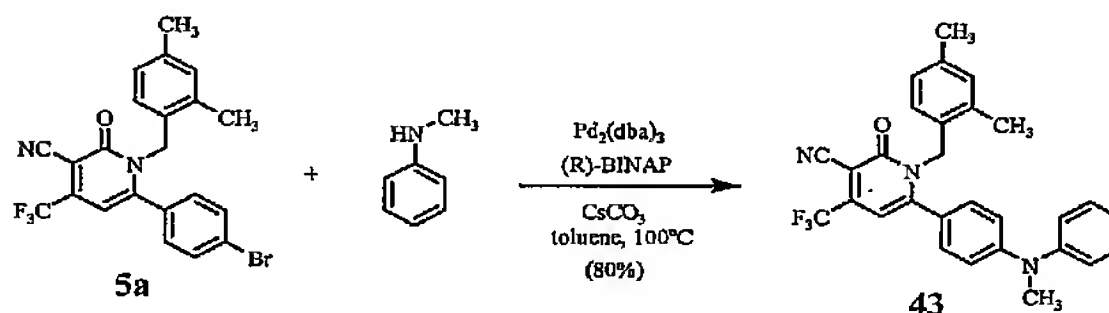
**42**

1-(2,4-Dimethyl-benzyl)-6-(4-hydroxymethyl-phenyl)-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile

¹H-NMR (CDCl₃): δ 7.39 (d, J=8.1Hz, 2H), 7.17 (d, J=8.1Hz, 2H), 6.95 (bd, J=7.8Hz, 1H), 6.91 (bs, 1H), 6.60 (d, J=7.6Hz, 1H), 6.43 (s, 1H), 5.10 (s, 2H), 4.76 (bd, 2H), 2.28 (s, 3H), 1.94 (s, 3H).
 10 MS(ES⁺): 413.1 (M+H)

EXAMPLE 43

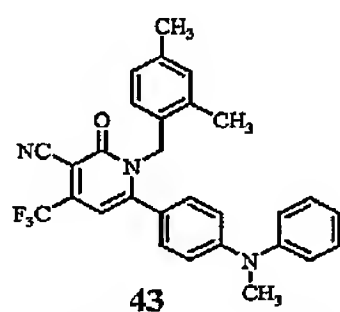
This example illustrates the preparation of compound **43**.



15 6-(4-Bromo-phenyl)-1-(2,4-dimethyl-benzyl)-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile **5a** (38 mg, 0.082 mmoles) was combined with N-methylaniline (11 μL, 0.10 mmoles) and 0.5 mL of anhydrous toluene within a 7 mL reaction vial. In a separate vial was added tris(dibenzylideneacetone) dipalladium (8 mg, 0.009 mmoles), (R)-BINAP (8

-290-

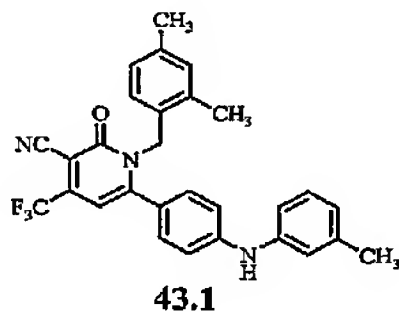
mg, 0.013 mmoles), cesium carbonate (38 mg, 0.12 mmoles) and 0.3 mL of anhydrous toluene. This "catalytic" mixture was stirred at room temperature for 5 min under dry-nitrogen. To the stirring "catalytic" solution under nitrogen was then added the "bromide" solution, and the resulting mixture was sealed under dry-nitrogen and was stirred at 100 °C for 16 hours. After this period the reaction mixture was purified directly using flash silica chromatography (0-20% EtOAc/Hexane) to provide 32 mg (80% yield) of 43 as an orange-red residue.



43
1-(2,4-Dimethyl-benzyl)-6-[4-(methyl-phenyl-amino)-phenyl]-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile

10 $^1\text{H-NMR}$ (CDCl_3): δ 7.44-7.34 (m, 2H), 7.25-7.14 (m, 3H), 7.07-7.02 (m, 2H), 6.97-6.92 (m, 2H), 6.72 (d, $J=9.1\text{Hz}$, 2H), 6.63 (d, $J=8.1\text{Hz}$, 1H), 6.46 (s, 1H), 5.18 (s, 2H), 3.33 (s, 3H), 2.28 (s, 3H), 2.10 (s, 3H). $\text{MS(ES}^+)$: 488.4 (M^+H)

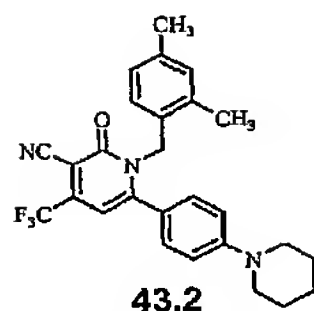
15 The following compounds were prepared in a manner similar to that described above.



43.1
1-(2,4-Dimethyl-benzyl)-2-oxo-6-(4-*m*-tolylamino-phenyl)-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile

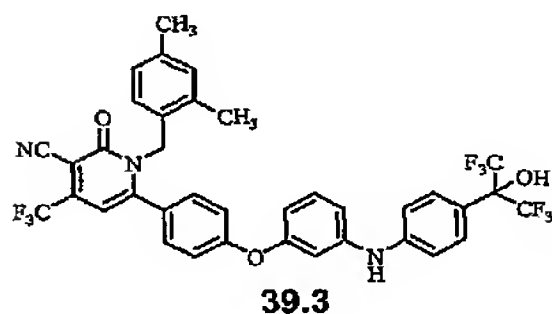
$\text{MS(ES}^+)$: 488.4 (M^+H)

-291-



1-(2,4-Dimethyl-benzyl)-2-oxo-6-(4-piperidin-1-yl-phenyl)-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile

MS(ES⁺): 466.4 (M+H)

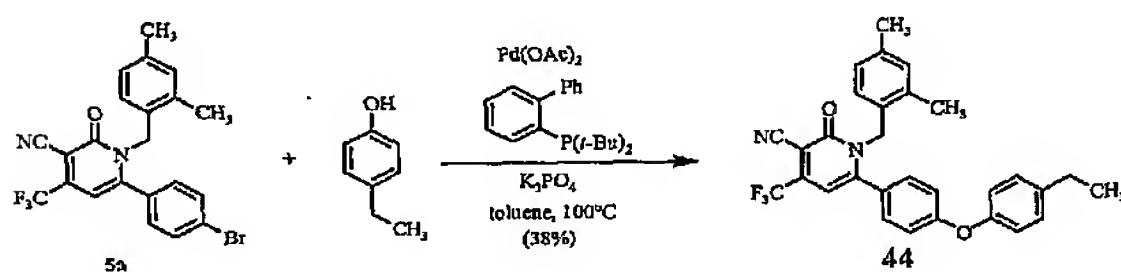


MS(ES⁺): 640.0 (M+H)

5

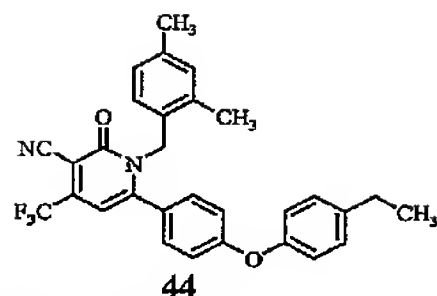
EXAMPLE 44

This example illustrates the preparation of compound **44**.



- 6-(4-Bromo-phenyl)-1-(2,4-dimethyl-benzyl)-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile **5a** (100 mg, 0.22 mmoles) was combined with 4-ethylphenol (32 mg, 0.26 mmoles), palladium acetate (5 mg, 0.022 mmoles), 2-(di-*t*-butylphosphino)biphenyl (12 mg, 0.040 mmoles), potassium phosphate (100 mg, 0.47 mmoles) and 1.0 mL of anhydrous toluene within an oven-dried 7 mL reaction vial. The mixture was sealed and stirred at 100 °C for 16 hours. After this period the mixture was purified directly using flash silica chromatography (0-20% EtOAc/Hexane) to yield 42 mg (38%) of **44** as a yellow residue.

-292-

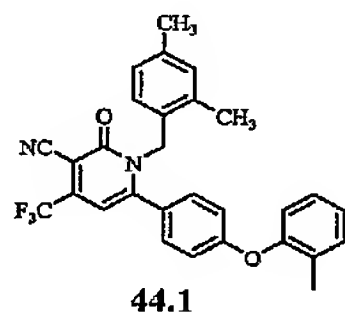


1-(2,4-Dimethyl-benzyl)-6-[4-(4-ethyl-phenoxy)-phenyl]-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile

¹H-NMR (CDCl₃): δ 7.21 (d, J=8.3Hz, 2H), 7.09 (d, J=8.3Hz, 2H), 6.98-6.89 (m, 6H), 6.60 (d, J=7.8Hz, 1H), 6.44 (s, 1H), 5.14 (s, 2H), 2.66 (q, J=7.6Hz, 2H), 2.27 (s, 3H), 2.01 (s, 3H), 1.25 (t, J=7.6Hz, 3H). MS(ES⁺): 503.2 (M+H)

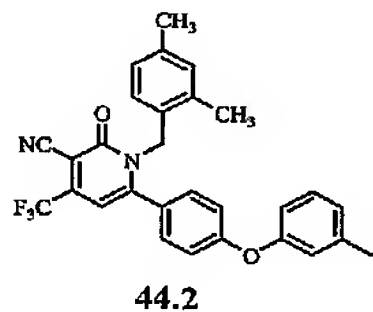
5

The following compounds were prepared in a manner similar to that described above.



1-(2,4-Dimethyl-benzyl)-2-oxo-6-(4-o-tolyloxy-phenyl)-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile

MS(ES⁺): 489.2 (M+H)

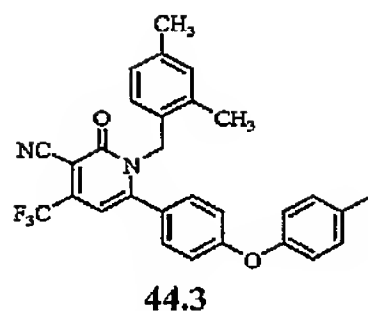


1-(2,4-Dimethyl-benzyl)-2-oxo-6-(4-m-tolyloxy-phenyl)-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile

MS(ES⁺): 489.4 (M+H)

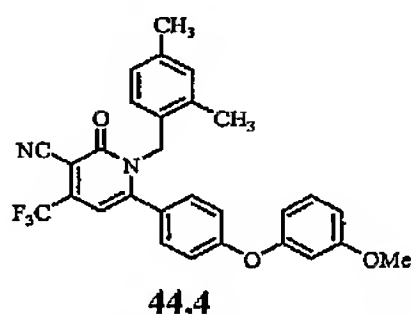
10

-293-



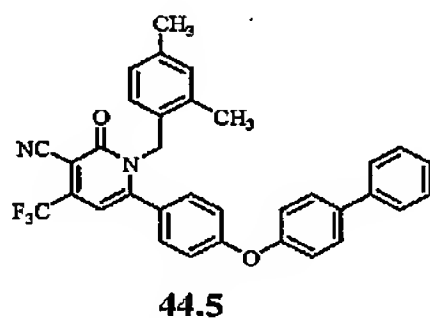
1-(2,4-Dimethyl-benzyl)-2-oxo-6-(4-*p*-
tolyloxy-phenyl)-4-trifluoromethyl-1,2-
dihydro-pyridine-3-carbonitrile

MS(ES⁺): 489.4 (M+H)



1-(2,4-Dimethyl-benzyl)-6-[4-(3-methoxy-
phenoxy)-phenyl]-2-oxo-4-trifluoromethyl-1,2-
dihydro-pyridine-3-carbonitrile

MS(ES⁺): 505.3 (M+H)

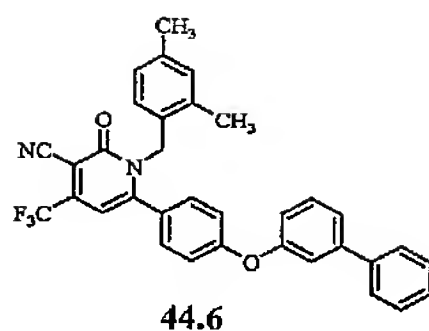


6-[4-(Biphenyl-4-yloxy)-phenyl]-1-(2,4-
dimethyl-benzyl)-2-oxo-4-trifluoromethyl-1,2-
dihydro-pyridine-3-carbonitrile

5

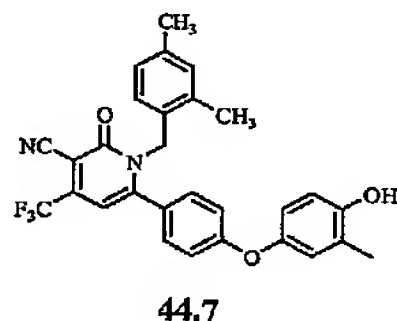
¹H-NMR (CDCl₃): δ 7.64-7.54 (m, 4H), 7.48-7.42 (m, 2H), 7.40-7.33 (m, 1H), 7.16-7.08 (m, 4H), 7.02-6.87 (m, 4H), 6.61 (d, J=7.8Hz, 1H), 6.46 (s, 1H), 5.15 (s, 2H), 2.28 (s, 3H), 2.02 (s, 3H).

-294-



6-[4-(Biphenyl-3-yloxy)-phenyl]-1-(2,4-dimethyl-benzyl)-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile

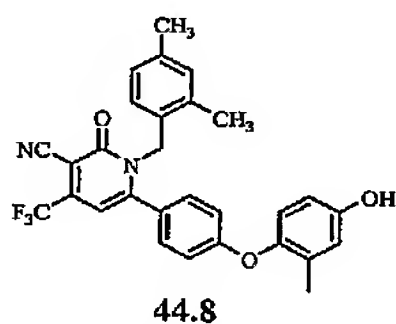
$^1\text{H-NMR}$ (CDCl_3): δ 7.59-7.53 (m, 2H), 7.49-7.35 (m, 4H), 7.15-7.09 (m, 2H), 7.05-6.88 (m, 5H), 6.61 (d, $J=8.1\text{Hz}$, 1H), 6.45 (s, 1H), 5.14 (s, 2H), 2.26 (s, 3H), 2.00 (s, 3H).



1-(2,4-Dimethyl-benzyl)-6-[4-(4-hydroxy-3-methyl-phenoxy)-phenyl]-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile

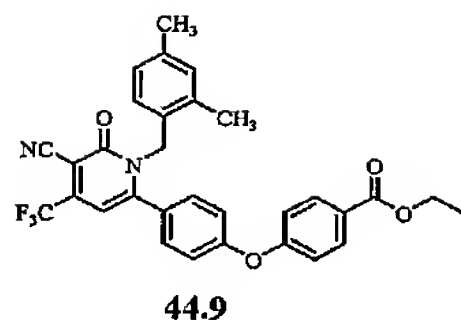
5

$\text{MS}(\text{ES}^+)$: 505.1 ($\text{M}+\text{H}$)



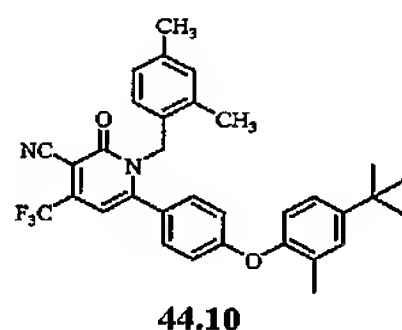
1-(2,4-Dimethyl-benzyl)-6-[4-(4-hydroxy-2-methyl-phenoxy)-phenyl]-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile

$\text{MS}(\text{ES}^+)$: 505.4 ($\text{M}+\text{H}$)

-295-

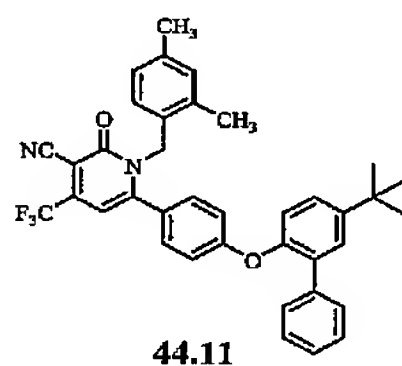
4-{4-[5-Cyano-1-(2,4-dimethyl-benzyl)-6-oxo-4-trifluoromethyl-1,6-dihydro-pyridin-2-yl]-phenoxy}-benzoic acid ethyl ester

MS(ES⁺): 547.4 (M+H)



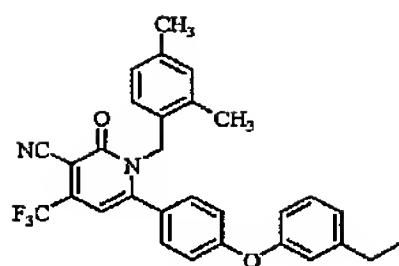
6-[4-(4-*tert*-Butyl-2-methyl-phenoxy)-phenyl]-1-(2,4-dimethyl-benzyl)-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile

MS(ES⁺): 545.2 (M+H)



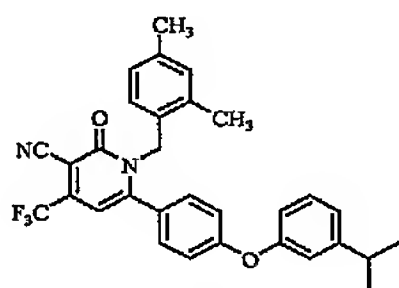
6-[4-(5-*tert*-Butyl-biphenyl-2-yloxy)-phenyl]-1-(2,4-dimethyl-benzyl)-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile

MS(ES⁺): 607.6 (M+H)

-296-**44.12**

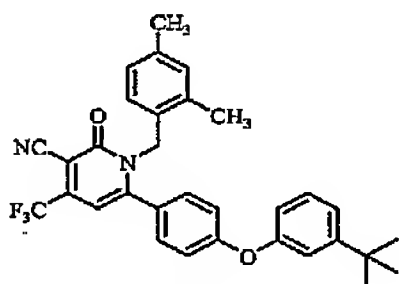
1-(2,4-Dimethyl-benzyl)-6-[4-(3-ethyl-phenoxy)-phenyl]-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile

MS(ES⁺): 503.0 (M+H)

**44.13**

1-(2,4-Dimethyl-benzyl)-6-[4-(3-isopropyl-phenoxy)-phenyl]-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile

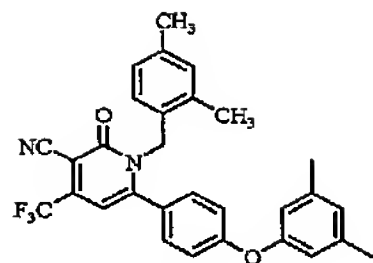
MS(ES⁺): 517.4 (M+H)

**44.14**

6-[4-(3-*tert*-Butyl-phenoxy)-phenyl]-1-(2,4-dimethyl-benzyl)-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile

MS(ES⁺): 531.3 (M+H)

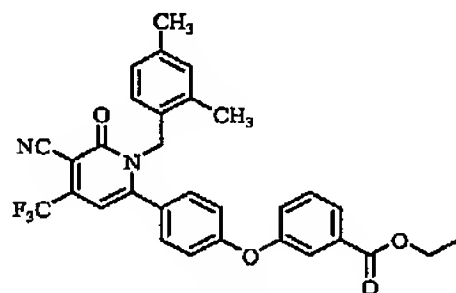
-297-



44.15

1-(2,4-Dimethyl-benzyl)-6-[4-(3,5-dimethyl-phenoxy)-phenyl]-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile

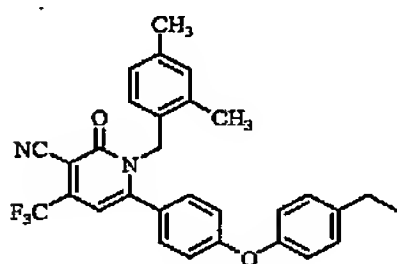
MS(ES⁺): 503.3 (M+H)



44.16

3-{4-[5-Cyano-1-(2,4-dimethyl-benzyl)-6-oxo-4-trifluoromethyl-1,6-dihydro-pyridin-2-yl]-phenoxy}-benzoic acid ethyl ester

MS(ES⁺): 547.3 (M+H)



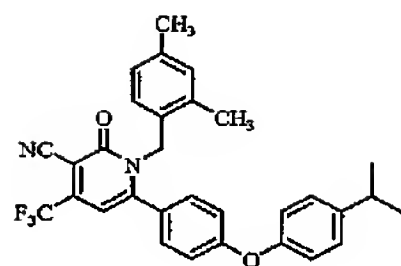
44.17

1-(2,4-Dimethyl-benzyl)-6-[4-(4-ethyl-phenoxy)-phenyl]-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile

5

¹H-NMR (CDCl₃): δ 7.21 (d, J=8.6Hz, 2H), 7.09 (d, J=8.6Hz, 2H), 6.98-6.89 (m, 6H), 6.60 (d, J=7.8 Hz, 1H), 6.44 (s, 1H), 5.14 (s, 2H), 2.66 (q, J=7.6Hz, 2H), 2.27 (s, 3H), 2.01 (s, 3H), 1.25 (t, J=7.6Hz, 3H).

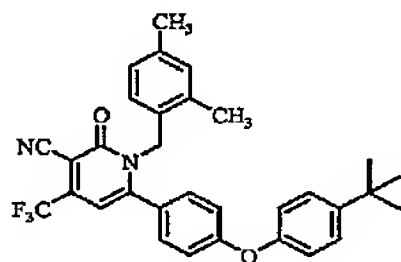
-298-



44.18

1-(2,4-Dimethyl-benzyl)-6-[4-(4-isopropyl-phenoxy)-phenyl]-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile

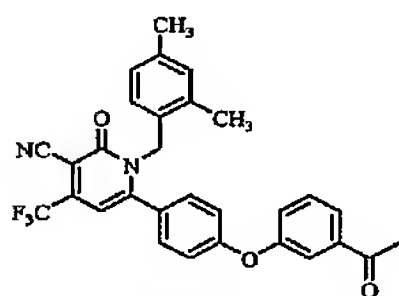
MS(ES⁺): 517.4 (M+H)



44.19

6-[4-(4-*tert*-Butyl-phenoxy)-phenyl]-1-(2,4-dimethyl-benzyl)-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile

MS(ES⁺): 531.4 (M+H)

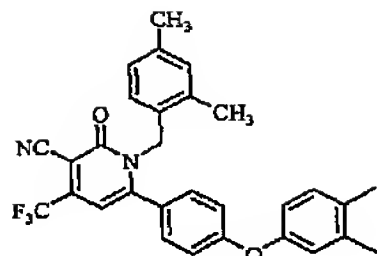


44.20

6-[4-(3-Acetyl-phenoxy)-phenyl]-1-(2,4-dimethyl-benzyl)-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile

MS(ES⁺): 517.5 (M+H)

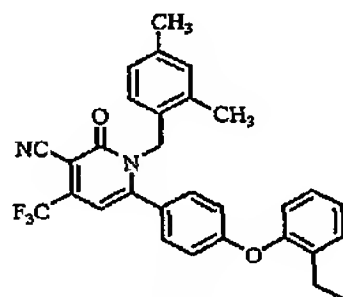
-299-



44.21

1-(2,4-Dimethyl-benzyl)-6-[4-(3,4-dimethyl-phenoxy)-phenyl]-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile

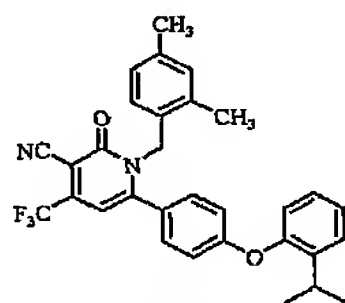
MS(ES⁺): 503.1 (M+H)



44.22

1-(2,4-Dimethyl-benzyl)-6-[4-(2-ethyl-phenoxy)-phenyl]-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile

MS(ES⁺): 503.3 (M+H)

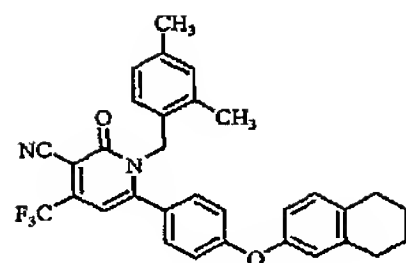


44.23

1-(2,4-Dimethyl-benzyl)-6-[4-(2-isopropyl-phenoxy)-phenyl]-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile

MS(ES⁺): 517.5 (M+H)

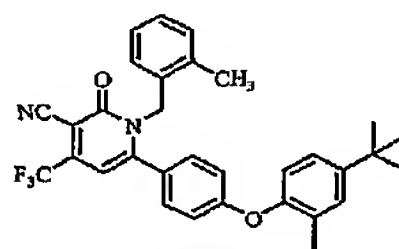
-300-



44.24

1-(2,4-Dimethyl-benzyl)-2-oxo-6-[4-(5,6,7,8-tetrahydro-naphthalen-2-yloxy)-phenyl]-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile

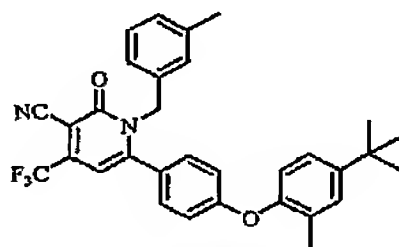
MS(ES⁺): 529.3 (M+H)



44.25

6-[4-(4-*tert*-Butyl-2-methyl-phenoxy)-phenyl]-1-(2-methyl-benzyl)-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile

MS(ES⁺): 531.2 (M+H)

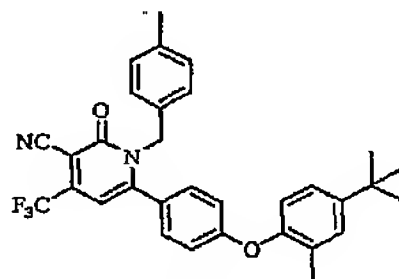


44.26

6-[4-(4-*tert*-Butyl-2-methyl-phenoxy)-phenyl]-1-(3-methyl-benzyl)-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile

5

MS(ES⁺): 531.3 (M+H)

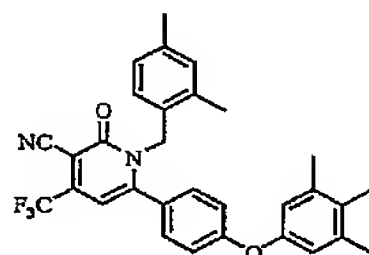


44.27

6-[4-(4-*tert*-Butyl-2-methyl-phenoxy)-phenyl]-1-(4-methyl-benzyl)-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile

-301-

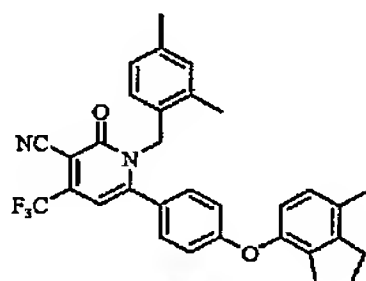
MS(ES⁺): 531.3 (M+H)



44.28

1-(2,4-Dimethyl-benzyl)-2-oxo-4-trifluoromethyl-6-[4-(3,4,5-trimethyl-phenoxy)-phenyl]-1,2-dihydro-pyridine-3-carbonitrile

MS(ES⁺): 517.4 (M+H)

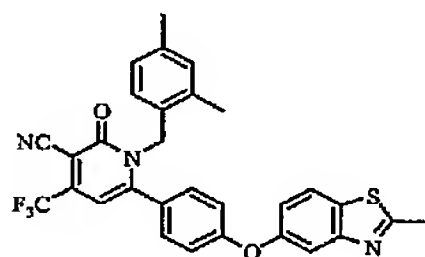


44.29

1-(2,4-Dimethyl-benzyl)-6-[4-(7-methyl-indan-4-yloxy)-phenyl]-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile

5

MS(ES⁺): 529.4 (M+H)

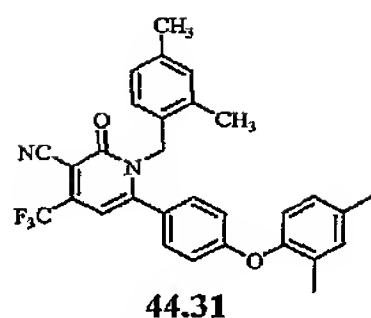


44.30

1-(2,4-Dimethyl-benzyl)-6-[4-(2-methyl-benzothiazol-5-yloxy)-phenyl]-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile

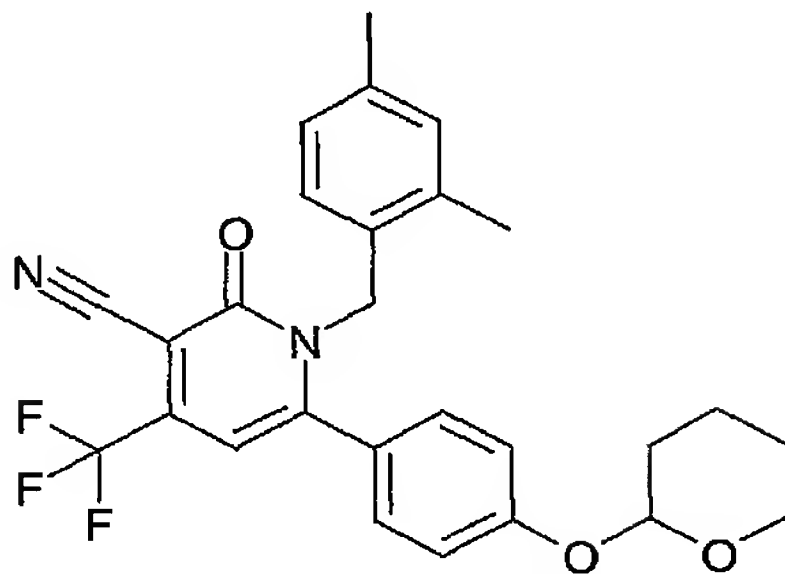
MS(ES⁺): 546.5 (M+H)

-302-



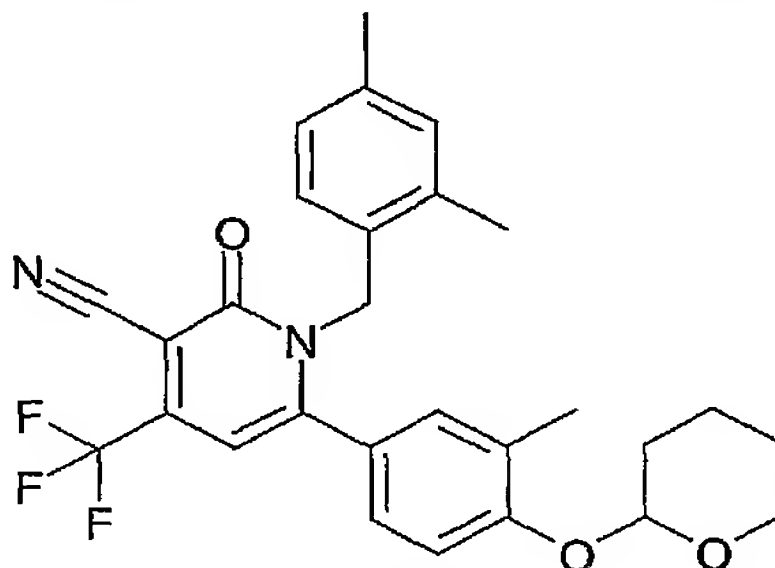
1-(2,4-Dimethyl-benzyl)-6-[4-(2,4-dimethyl-phenoxy)-phenyl]-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile

MS(ES⁺): 503.2 (M+H)



5 1-(2,4-Dimethyl-benzyl)-2-oxo-6-[4-(tetrahydro-pyran-2-yloxy)-phenyl]-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile

¹H-NMR (CDCl₃): δ7.10 (m, 2 H), 7.02 (m, 2 H), 6.94 (m, 2 H), 6.61 (m, 1 H), 6.44 (s, 1 H), 5.45 (m, 1 H), 5.13 (s, 2 H), 3.83 (m, 1 H), 3.61 (m, 1 H), 2.28 (s, 3 H), 2.00 (s, 3 H), 1.87 (m, 2 H), 1.87 (m, 2 H), 1.68 (m, 4 H).



-303-

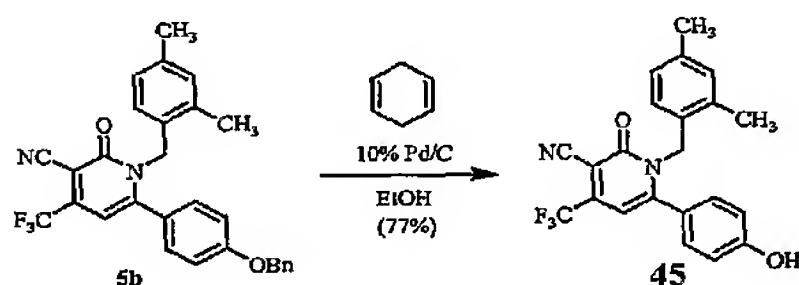
1-(2,4-Dimethyl-benzyl)-6-[3-methyl-4-(tetrahydro-pyran-2-yloxy)-phenyl]-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile

¹H-NMR (CDCl₃): 87.03 (m, 1 H), 6.95 (m, 2 H), 6.91 (m, 1 H), 6.86 (m, 1 H), 6.63 (m, 1 H), 6.42 (s, 1 H), 5.46 (m, 1 H), 5.11 (m, 2 H), 3.79 (m, 1 H), 3.60 (m, 1 H), 2.27 (s, 3 H), 2.14 (s, 3 H), 2.01 (m, 1 H), 1.97 (s, 3 H), 1.89 (m, 2 H), 1.68 (m, 2 H), 1.60 (m, 1 H).

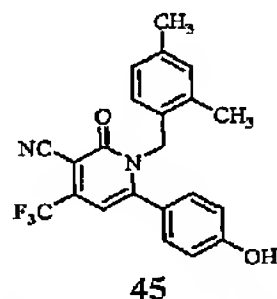
10

EXAMPLE 45

15 This example illustrates the preparation of compound 45.



6-(4-Benzyloxy-phenyl)-1-(2,4-dimethyl-benzyl)-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile **5b** (0.55 g, 1.13 mmol) was combined with cyclohexadiene (1.6 mL, 16.9 mmol), 10% Pd/C (0.6 g) and 10 mL of anhydrous EtOH. This mixture was then stirred at room temperature for 24 hours. After this period the reaction mixture was vacuum filtered through Celite and the resulting filtrate was evaporated *in vacuo* to yield 0.35 g (77%) of **45** as a yellowish/orange solid.

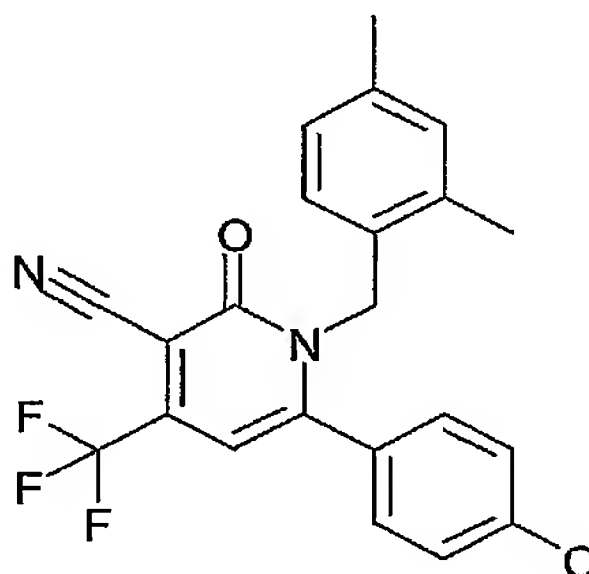


1-(2,4-Dimethyl-benzyl)-6-(4-hydroxy-phenyl)-
2-oxo-4-trifluoromethyl-
1,2-dihydropyridine-3-carbonitrile

-304-

$^1\text{H-NMR}$ (CDCl_3): δ 7.04 (d, $J=8.6\text{Hz}$, 2H), 6.95 (d, $J=7.6\text{Hz}$, 1H), 6.92 (s, 1H), 6.80 (d, $J=7.6\text{Hz}$, 2H), 6.60 (d, $J=7.8\text{Hz}$, 1H), 6.43 (s, 1H), 5.47 (bs, 1H), 5.12 (s, 2H), 2.28 (s, 3H), 1.98 (s, 3H).

Following compounds were prepared in manner similar to that described above.

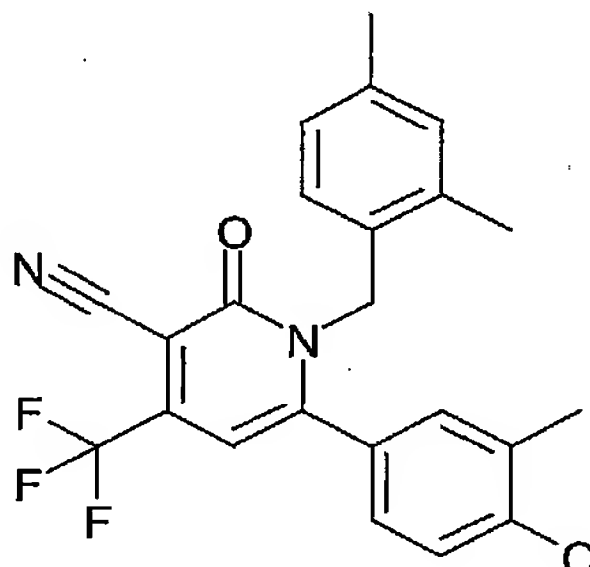


45.1

1-(2,4-Dimethyl-benzyl)-6-(4-hydroxy-phenyl)-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile

10

$^1\text{H-NMR}$ (Acetone- d_6): δ 8.92 (s, 1 H), 7.14 (m, 2 H), 6.85 (m, 2 H), 6.76 (m, 2 H), 6.64 (m, 1 H), 6.50 (s, 1 H), 5.08 (s, 2 H), 2.11 (s, 3 H), 1.92 (s, 3 H).



45.2

15 1-(2,4-Dimethyl-benzyl)-6-(4-hydroxy-3-methyl-phenyl)-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile

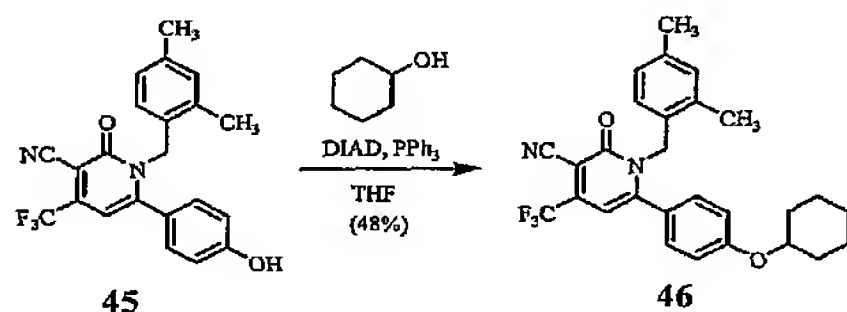
$^1\text{H-NMR}$ (CDCl_3): δ 6.91 – 6.78 (m, 4 H), 6.66 (m, 1 H), 6.56 (m, 1 H), 6.35 (s, 1 H), 5.05 (s, 2 H), 2.22 (s, 3 H), 2.07 (s, 3 H), 1.90 (s, 3 H).

20

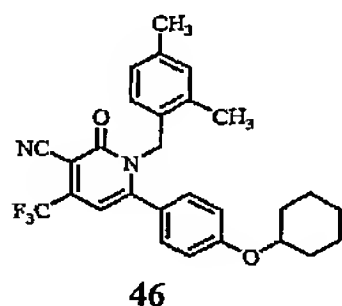
-305-

EXAMPLE 46

This example illustrates the preparation of compound **46**.



- 1- (2,4-Dimethyl-benzyl)-6-(4-hydroxy-phenyl)-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile **45** (31 mg, 0.078 mmoles) was combined with triphenylphosphine (29 mg, 0.11 mmoles) in 1.0 mL of anhydrous THF. To this stirring mixture at room temperature was slowly added (over 1 hour using a syringe pump) a solution of cyclohexanol (12 μ L, 0.11 mmoles) and diisopropyl azodicarboxylate (22 μ L, 0.11 mmoles) in 1.0 mL of anhydrous THF. The mixture was then stirred at room temperature for 24 hours. After this period the reaction mixture was purified directly using flash silica chromatography (0-20% EtOAc/Hexane) to yield 18 mg (48%) of **46** as a yellow residue.

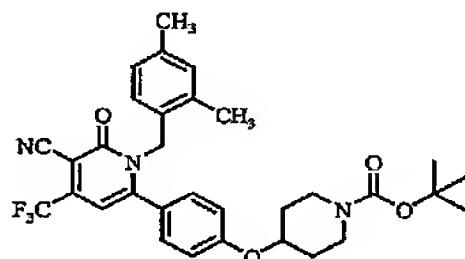


6-(4-Cyclohexyloxy-phenyl)-1-(2,4-dimethyl-benzyl)-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile

- ¹H-NMR (CDCl₃): δ 7.08 (d, J=8.6Hz, 2H), 6.97-6.91 (m, 2H), 6.85 (d, J=8.6Hz, 2H), 6.61 (d, J=7.8Hz, 1H), 6.44 (s, 1H), 5.14 (s, 2H), 4.32-4.23 (m, 1H), 2.29 (s, 3H), 2.00 (s, 3H), 1.99-1.22 (m, 10H).
MS(ES⁺): 481.4 (M+H)

-306-

The following compounds were prepared in a manner similar to that described above.

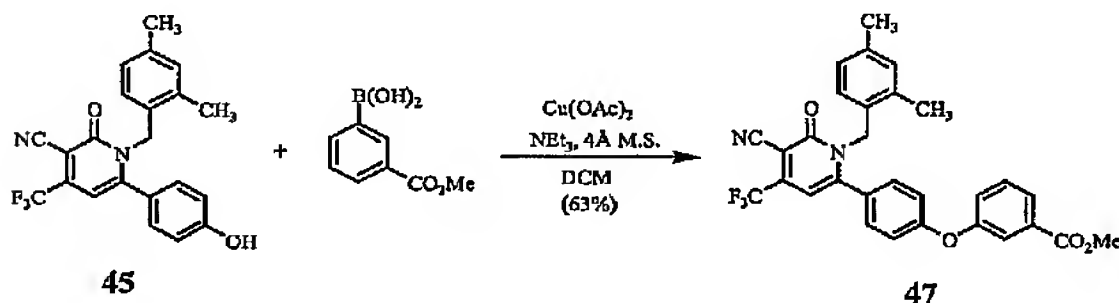
**46.1**

4-{4-[5-Cyano-1-(2,4-dimethyl-benzyl)-6-oxo-4-trifluoromethyl-1,6-dihydro-pyridin-2-yl]-phenoxy}-piperidine-1-carboxylic acid *tert*-butyl ester

MS(ES⁺): 582.3 (M+H)

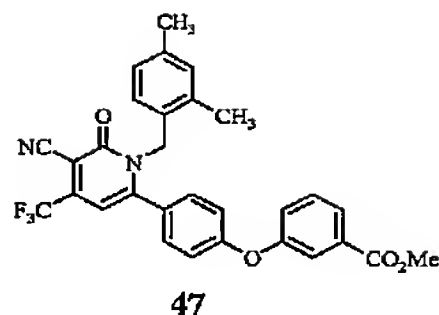
5**EXAMPLE 47**

This example illustrates the preparation of compound **47**.



- 1-(2,4-Dimethyl-benzyl)-6-(4-hydroxy-phenyl)-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile **45** (43 mg, 0.11 mmoles) was combined with (3-methoxycarbonylphenyl) boronic acid (62 mg, 0.34 mmoles), copper acetate (22 mg, 0.12 mmoles), 4Å molecular sieves (0.18 g) and 1.0 mL of anhydrous DCM within an oven-dried reaction vial. The mixture was stirred at room temperature for 15 min. After this period triethylamine (75 µL, 0.54 mmoles) was added and the mixture was stirred at room temperature for 16 hours. After this period the reaction mixture was purified directly using flash silica chromatography (0-20% EtOAc/Hexane) to yield 38 mg (63%) of **47** as a yellow residue.

-307-

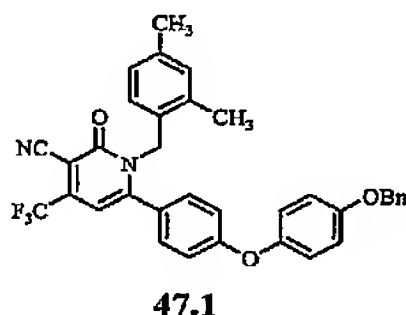


3-{4-[5-Cyano-1-(2,4-dimethyl-benzyl)-6-oxo-4-trifluoromethyl-1,6-dihydro-pyridin-2-yl]-phenoxy}-benzoic acid methyl ester

¹H-NMR (CDCl₃): δ 7.90-7.85 (m, 1H), 7.71-7.68 (m, 1H), 7.47 (t, J=7.8Hz, 1H), 7.27-7.23 (m, 1H), 7.12 (d, J=8.8Hz, 2H), 6.98-6.91 (m, 4H), 6.61 (d, J=7.8Hz, 1H), 6.45 (s, 1H), 5.14 (s, 2H), 3.92 (s, 3H), 2.27 (s, 3H), 2.01 (s, 3H). MS(ES⁺): 533.2 (M+H)

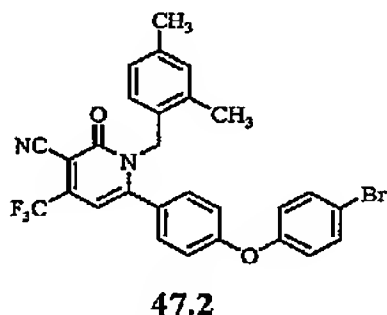
5

The following compounds were prepared in a manner similar to that described above.



6-[4-(4-Benzyloxy-phenoxy)-phenyl]-1-(2,4-dimethyl-benzyl)-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile

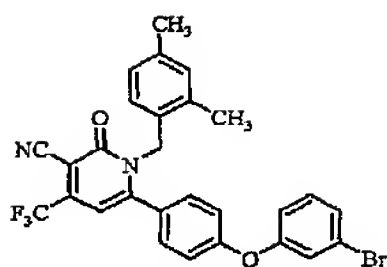
MS(ES⁺): 581.3 (M+H)



6-[4-(4-Bromo-phenoxy)-phenyl]-1-(2,4-dimethyl-benzyl)-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile

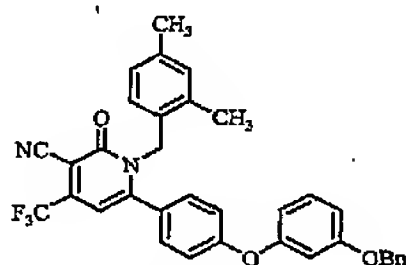
MS(ES⁺): 555.2 (M+H)

10

-308-**47.3**

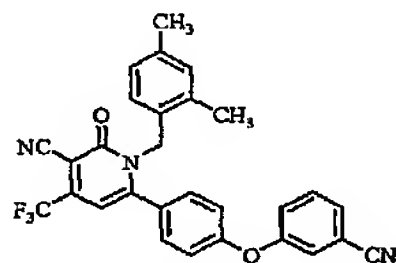
6-[4-(3-Bromo-phenoxy)-phenyl]-1-(2,4-dimethyl-benzyl)-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile

MS(ES⁺): 555.3 (M+H)

**47.4**

6-[4-(3-Benzyloxy-phenoxy)-phenyl]-1-(2,4-dimethyl-benzyl)-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile

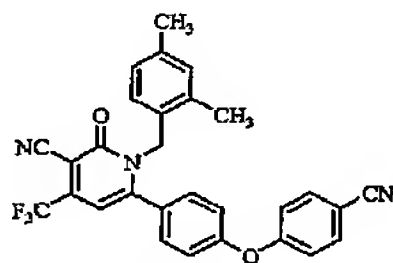
MS(ES⁺): 581.5 (M+H)

**47.5**

6-[4-(3-Cyano-phenoxy)-phenyl]-1-(2,4-dimethyl-benzyl)-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile

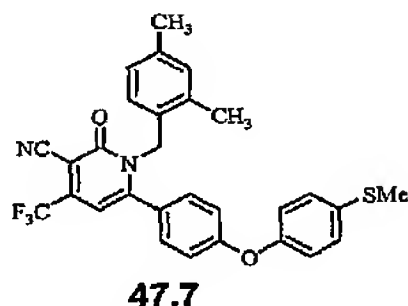
5

MS(ES⁺): 500.4 (M+H)

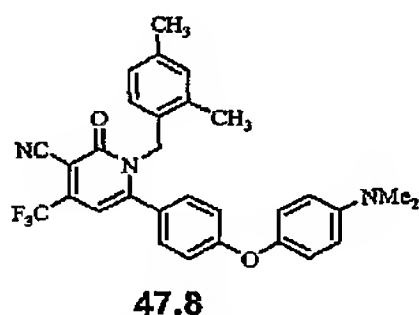
**47.6**

6-[4-(4-Cyano-phenoxy)-phenyl]-1-(2,4-dimethyl-benzyl)-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile

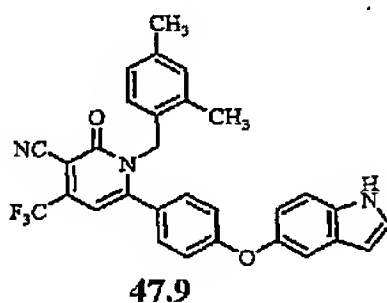
-309-

MS(ES⁺): 500.4 (M+H)

1-(2,4-Dimethyl-benzyl)-6-[4-(4-methylsulfanyl-phenoxy)-
phenyl]-2-oxo-4-trifluoromethyl-1,2-dihydro-
pyridine-3-carbonitrile

MS(ES⁺): 521.1 (M+H)

6-[4-(4-Dimethylamino-phenoxy)-phenyl]-1-(2,4-dimethyl-benzyl)-
2-oxo-4-trifluoromethyl-1,2-dihydro-p
yridine-3-carbonitrile

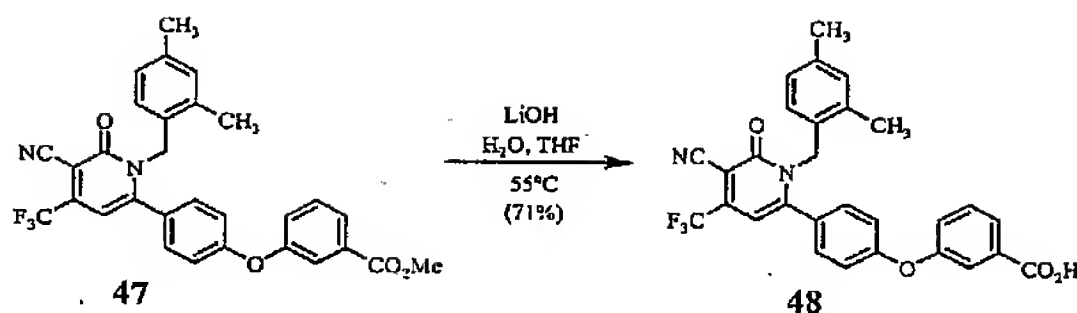
5MS(ES⁺): 518.4 (M+H)

1-(2,4-Dimethyl-benzyl)-6-[4-(1*H*-indol-5-yloxy)-phenyl]-2-oxo-
4-trifluoromethyl-1,2-dihydro-pyridi
ne-3-carbonitrile

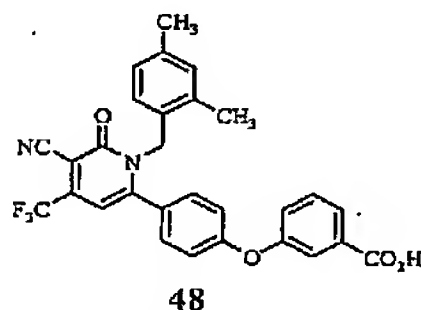
MS(ES⁺): 514.4 (M+H)**EXAMPLE 48**

This example illustrates the preparation of compound **48**.

-310-



- 3-{4-[5-Cyano-1-(2,4-dimethyl-benzyl)-6-oxo-4-trifluoromethyl-1,6-dihydro-pyridin-2-yl]-phenoxy}-benzoic acid methyl ester **47** (0.55 g, 1.01 mmol) was combined with lithium hydroxide (monohydrate, 93 mg, 2.22 mmol) in 10 mL of THF/H₂O (4:1). This mixture was then heated at 55 °C for 12 hours. After this period the mixture was evaporated *in vacuo* (-THF) and was combined with 1N HCl (10 mL). The aqueous acidic mixture was combined with enough NaCl to affect saturation and was extracted with Et₂O (4x20 mL). The combined ether layer was washed with brine, dried over Na₂SO₄, and was evaporated *in vacuo* to yield crude product. The crude product was purified using flash silica chromatography (0-60% EtOAc/Hexane) to yield 0.37g (71%) of product as a yellow residue.



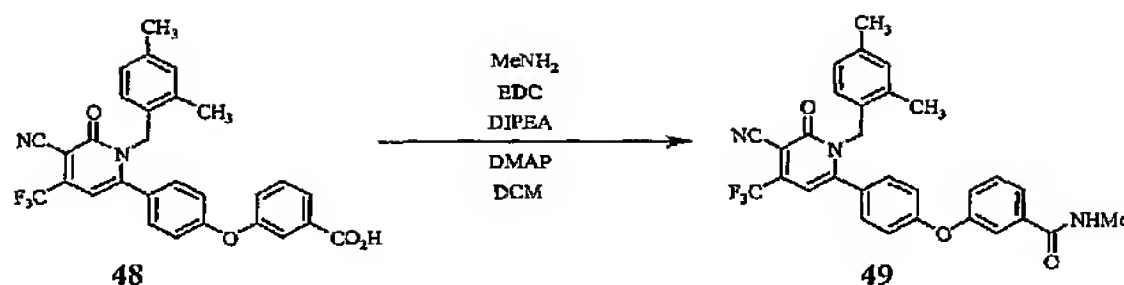
3-{4-[5-Cyano-1-(2,4-dimethyl-benzyl)-6-oxo-4-trifluoromethyl-1,6-dihydro-pyridin-2-yl]-phenoxy}-benzoic acid

- ¹H-NMR (CDCl₃): δ 7.95-7.91 (m, 1H), 7.74-7.71 (m, 1H), 7.51 (t, J=7.8Hz, 1H), 7.33-7.28 (m, 1H), 7.15-7.10 (m, 2H), 7.00-6.91 (m, 4H), 6.61 (d, J=8.1Hz, 1H), 6.46 (s, 1H), 5.14 (s, 2H), 2.27 (s, 3H), 2.00 (s, 3H). MS(ES⁺): 519.3 (M+H)

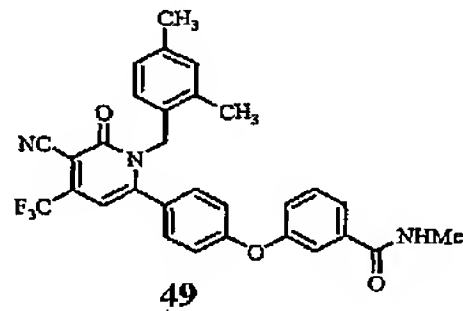
EXAMPLE 49

This example illustrates the preparation of compound **49**.

-311-



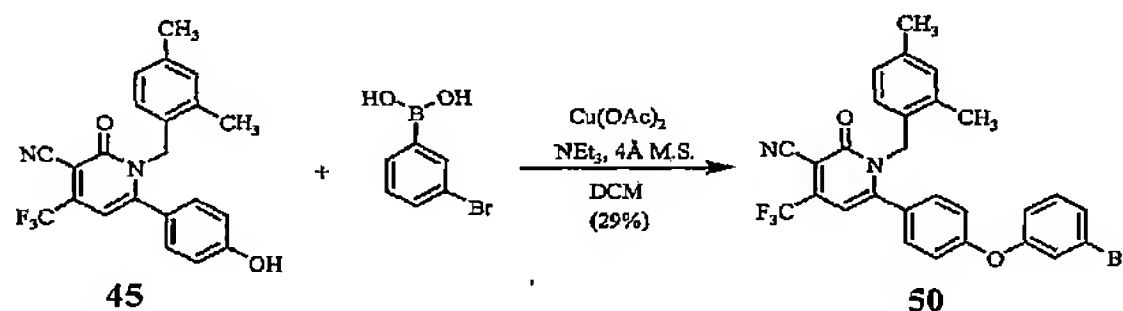
3-{4-[5-Cyano-1-(2,4-dimethyl-benzyl)-6-oxo-4-trifluoromethyl-1,6-dihydro-pyridin-2-yl]-phenoxy}-benzoic acid **48** (15 mg, 0.029 mmoles) was combined with 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride (EDC, 14 mg, 0.073 mmoles), 4-dimethylaminopyridine (DMAP, 2 mg, 0.016 mmoles) in 5 mL of anhydrous DCM. To this mixture was added diisopropylethylamine (DIPEA, 13 μ L, 0.075 mmoles) and methylamine ([2.0 M] solution in THF, 36 μ L, 0.72 mmoles). This mixture was then stirred at room temperature for 16 hours. After this period the reaction mixture was purified directly using flash silica chromatography (0-60% EtOAc/Hexane) to yield 13 mg (84% yield) of **49** as a yellow solid.



$^1\text{H-NMR}$ (CDCl_3): δ 7.52-7.41 (m, 3H), 7.19-7.10 (m, 3H), 6.98-6.91 (m, 4H), 6.61 (d, $J=7.6\text{Hz}$, 1H), 6.45 (s, 1H), 6.09 (bs, 1H), 5.14 (s, 2H), 3.01 (d, $J=5.1\text{Hz}$, 3H), 2.27 (s, 3H), 2.01 (s, 3H).

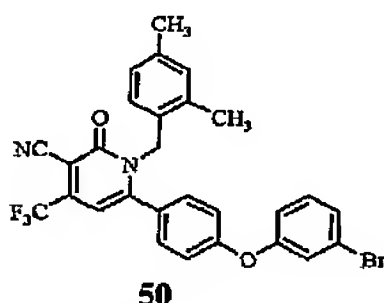
EXAMPLE 50

This example illustrates the preparation of compound **50**.



-312-

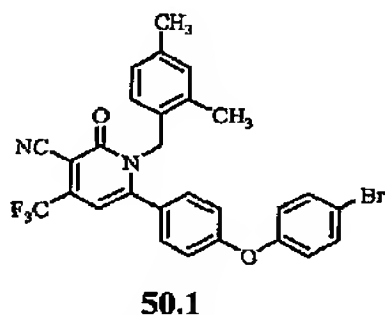
1-(2,4-Dimethyl-benzyl)-6-(4-hydroxy-phenyl)-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile **45** (104 mg, 0.26 mmoles) was combined with (3-bromophenyl) boronic acid (157mg, 0.78 mmoles), copper acetate (57 mg, 0.31 mmoles), 4Å molecular sieves (0.20g) and 1.0 mL of anhydrous DCM within an oven-dried reaction vial. The mixture was stirred at room temperature for 15 min. After this period triethylamine (182 µL, 1.31 mmoles) was added and the mixture was stirred at room temperature for 16 hours. After this period the reaction mixture was purified directly using flash silica chromatography (0-20% EtOAc/Hexane) to yield 41mg (29%) of **50** as a yellow residue.



6-[4-(3-Bromo-phenoxy)-phenyl]-1-(2,4-dimethyl-benzyl)-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile

MS(ES⁺): 555.3 (M+H)

The following compounds were prepared in a manner similar to that described above.



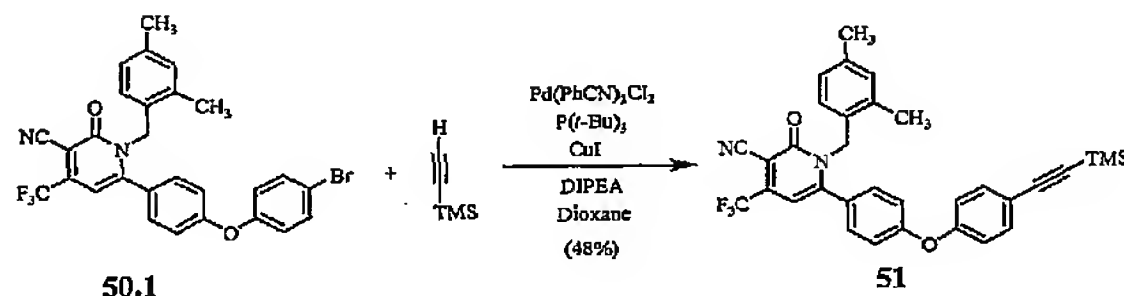
6-[4-(4-Bromo-phenoxy)-phenyl]-1-(2,4-dimethyl-benzyl)-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile

MS(ES⁺): 555.2 (M+H)

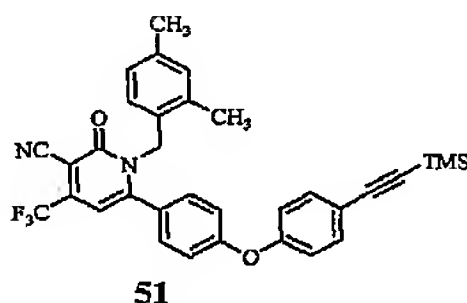
EXAMPLE 51

-313-

This example illustrates the preparation of compound **51**.



6-[4-(4-Bromo-phenoxy)-phenyl]-1-(2,4-dimethyl-benzyl)-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile **50.1** (108 mg, 0.195 mmols) was combined with dichlorobis(benzonitrile)palladium (II) (11 mg, 0.029 mmols), tri-*t*-butylphosphine (33 mg, 0.065 mmols), copper iodide (4 mg, 0.021 mmols), diisopropylethylamine (33 μ L, 0.24 mmols) and trimethylsilylacetylene (0.23 mmols) in 2.0 mL of anhydrous and thoroughly degassed dioxane. This mixture was then stirred at 50 °C for 24 hours. After this period the reaction mixture was evaporated and purified directly for flash silica chromatography (0-20% EtOAc/Hexane) to yield 53 mg (48% yield) of **51** as a yellow residue.



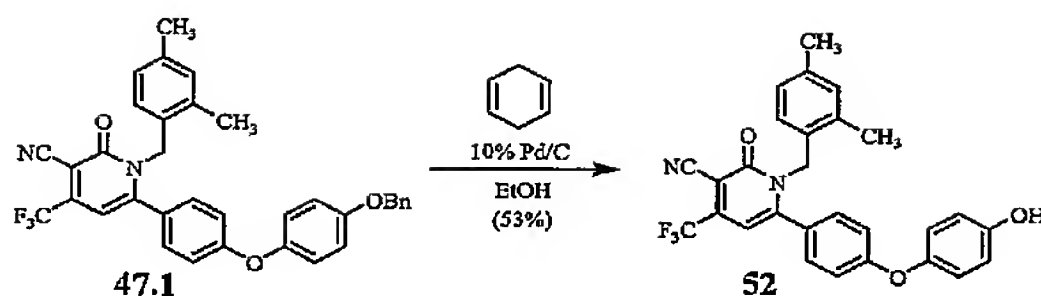
1-(2,4-Dimethyl-benzyl)-2-oxo-4-trifluoromethyl-6-[4-(4-trimethylsilylanyethynyl-phenoxy)-phenyl]-1,2-dihydro-pyridine-3-carbonitrile

$^1\text{H-NMR}$ (CDCl_3): δ 7.52-7.46 (m, 2H), 7.14-7.09 (m, 2H), 6.97-6.89 (m, 6H), 6.60 (d, $J=8.1\text{Hz}$, 1H), 6.44 (s, 1H), 5.13 (s, 2H), 2.28 (s, 3H), 1.99 (s, 3H), 0.25 (s, 9H).

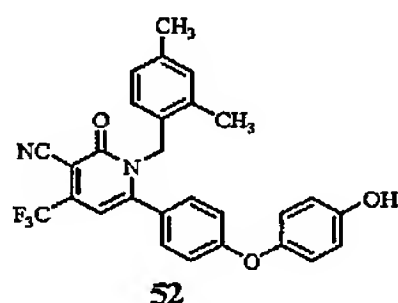
EXAMPLE 52

This example illustrates the preparation of compound **52**.

-314-



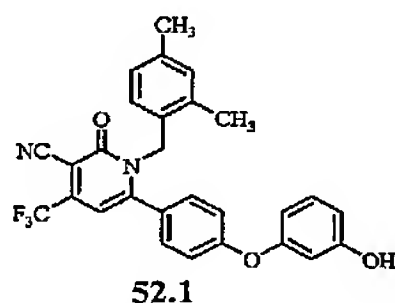
5 6-[4-(4-Benzyloxy-phenoxy)-phenyl]-1-(2,4-dimethyl-benzyl)-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile **47.1** (29 mg, 0.05 mmoles) was combined with cyclohexadiene (0.1 mL, 1.05 mmoles), 10% Pd/C (50 mg) and 10 mL of anhydrous EtOH. This mixture was then stirred at room temperature for 24 hours. After this period the reaction mixture was vacuum filtered through Celite and the resulting filtrate was evaporated *in vacuo* to yield 13 mg (53%) of **52** as a yellow residue.



1-(2,4-Dimethyl-benzyl)-6-[4-(4-hydroxy-phenoxy)-phenyl]-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile

10 $^1\text{H-NMR}$ (CDCl_3): δ 7.12-7.06 (m, 2H), 6.97-6.82 (m, 8H), 6.59 (d, $J=7.8\text{Hz}$, 1H), 6.44 (s, 1H), 5.13 (s, 2H), 4.84 (s, 1H), 2.28 (s, 3H), 2.01 (s, 3H). MS(ES $^+$): 519.3 (M+H)

The following compounds were prepared in a manner similar to that described above.

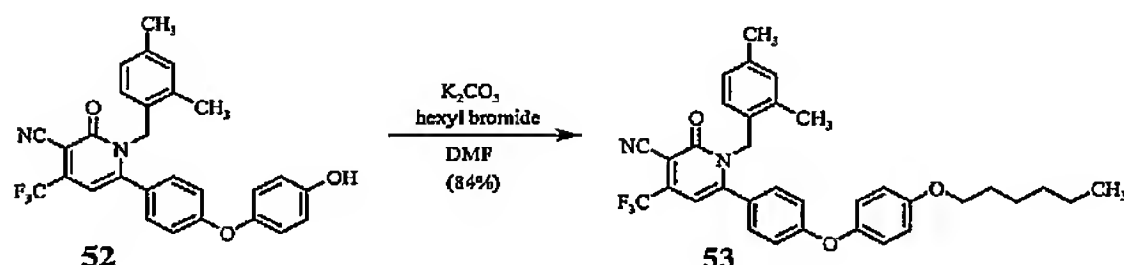


15 1-(2,4-Dimethyl-benzyl)-6-[4-(3-hydroxy-phenoxy)-phenyl]-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile

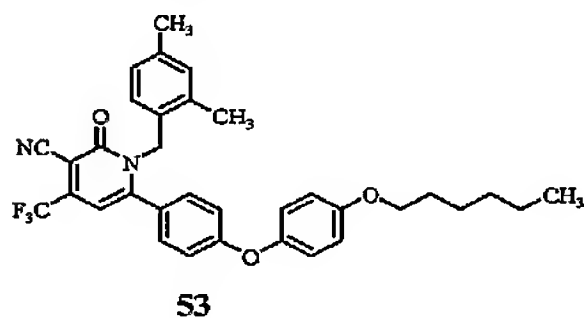
-315-

MS(ES⁺): 519.3 (M+H)**EXAMPLE 53**

This example illustrates the preparation of compound **53**.

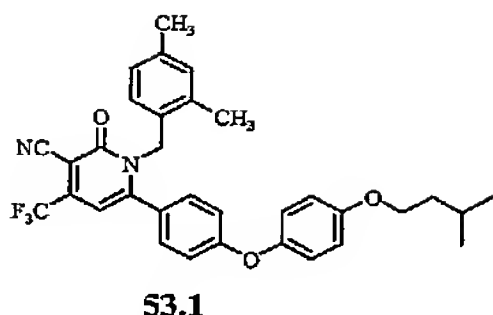


- 5** 1-(2,4-Dimethyl-benzyl)-6-[4-(4-hydroxy-phenoxy)-phenyl]-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile **52** (16 mg, 0.033 mmoles) was combined with potassium carbonate (23 mg, 0.166 mmoles) and hexyl bromide (20 μ L, 0.142 mmoles) in 2.0 mL of anhydrous DMF. This mixture was stirred at room temperature for 24 hours. After this period the reaction
- 10** mixture was combined with 50 mL of water and was extracted with EtOAc (4x15 mL). The combined EtOAc layer was washed with water (4x15 mL) and 15 mL of brine. The resulting EtOAc later was dried over anhydrous Na₂SO₄ and was evaporated *in vacuo* to yield the crude product. The crude product was purified using flash silica chromatography (0-20% EtOAc/Hexane) to yield
- 15** 14 mg (84%) of **53** as a yellow residue.

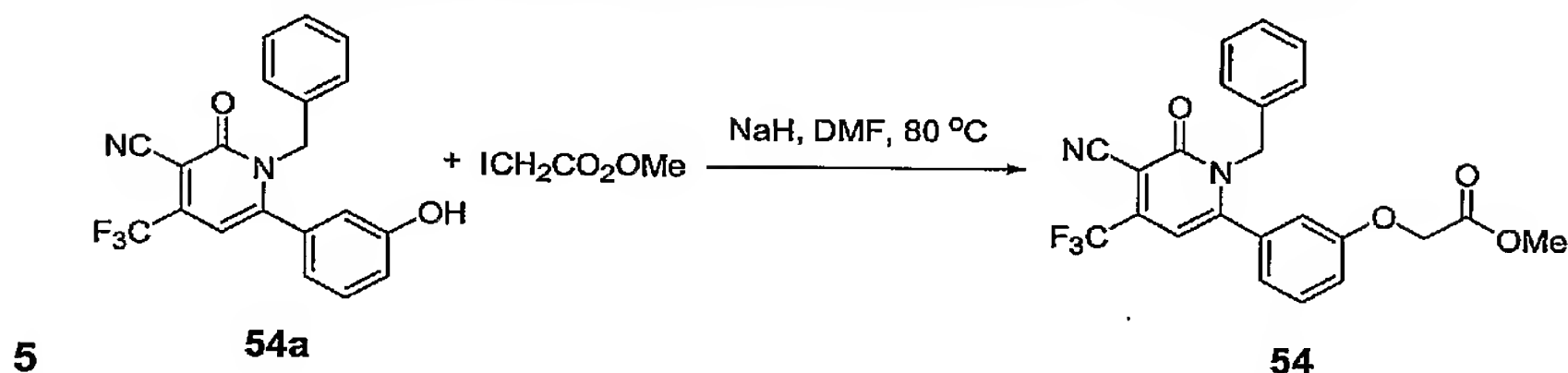


- ¹H-NMR (CDCl₃): δ 7.05 (d, J=8.8Hz, 2H), 6.97-6.81 (m, 8H), 6.57 (d, J=7.3Hz, 1H), 6.40 (s, 1H), 5.10 (s, 2H), 3.92 (t, J=6.6Hz, 2H), 2.24 (s, 3H), 1.98 (s, 3H), 1.81-1.71 (m, 2H), 1.49-1.39 (m, 2H), 1.35-1.28 (m, 4H), 0.91-0.84 (m, 3H). MS(ES⁺): 575.5 (M+H)
- 20**

-316-

MS(ES⁺): 561.3 (M+H)**EXAMPLE 54**

This example illustrates the preparation of compound **54**.

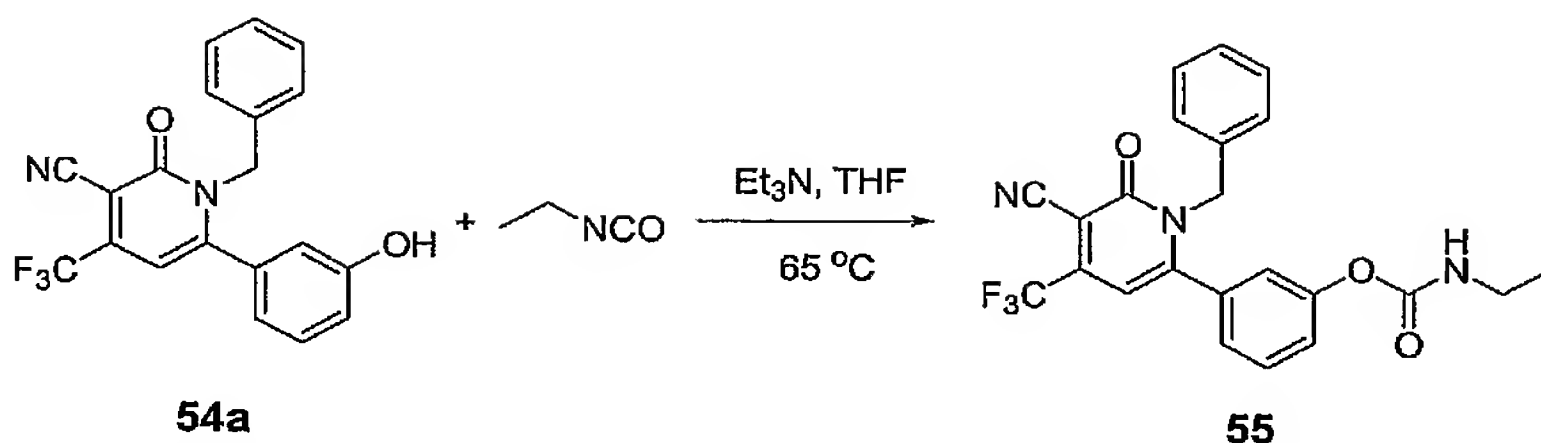


Sodium hydride (18 mg, 0.43 mmol) was added to a solution of **54a** (80 mg, 0.22 mmol) and methyl 2-iodoacetate (82 μ L, 0.86 mmol) in anhydrous DMF (2 mL). The reaction mixture was stirred under nitrogen atmosphere at 80 $^\circ$ C overnight. After the reaction mixture was cooled off, it was poured into 20 mL of water and extract with ethyl acetate (3 x 30 mL). The combined organic layer was washed with brine and water and concentrated *in vacuo*. The crude product was purified by column chromatography (40% ethyl acetate in hexane), providing product **54** (67 mg, 70% yield). ¹H-NMR (CDCl₃): δ 7.37 (m, 1H), 7.26 (m, 4 H), 7.06 (m, 1 H), 6.91 (m, 1 H), 6.82 (m, 1 H), 6.62 (m, 1 H), 6.40 (s, 1 H), 5.24 (s, 2 H), 4.46 (s, 2 H), 3.80 (s, 2 H).

EXAMPLE 55

This example illustrates the preparation of compound **55**.

-317-

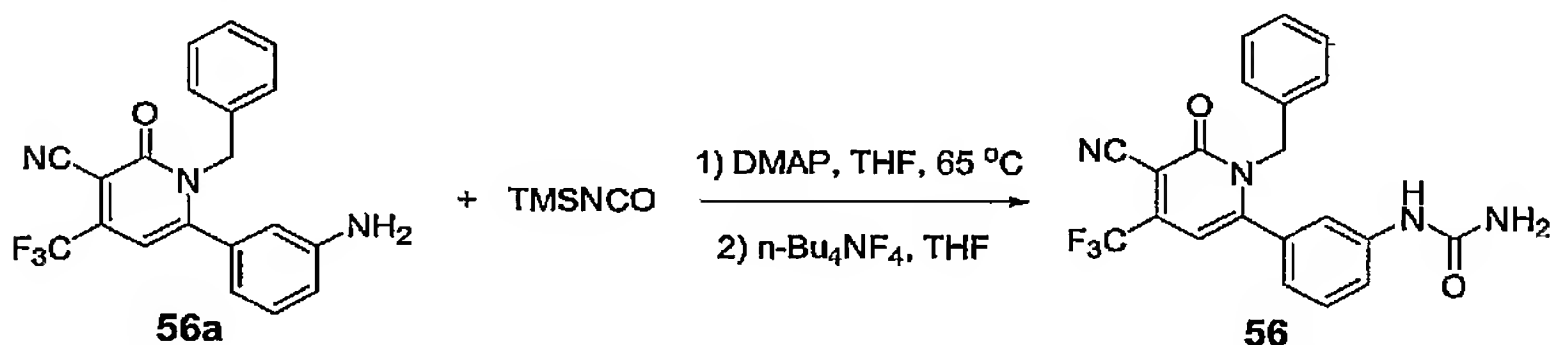


To a solution of **54a** (80 mg, 0.22 mmol) and triethylamine (60 μ L, 0.43 mmol) in anhydrous THF (2 mL) was added ethyl isocyanate (43 μ L, 0.54 mmol). The reaction mixture was stirred at 65 °C under nitrogen atmosphere for overnight. The reaction mixture was then cooled off and concentrated *in vacuo*. The crude product was purified by column chromatography (40% ethyl acetate in hexane) to yield product **55** (91 mg, 95% yield). $^1\text{H-NMR}$ (CDCl_3): δ 7.39 (m, 1 H), 7.29 (m, 1 H), 7.24-7.20 (m, 3 H), 7.04 (m, 1 H), 6.91 (m, 3 H), 6.41 (s, 1 H), 5.29 (s, 2 H), 5.05 (s, 1 H), 3.33 (m, 2 H), 1.24 (t, 7.1 Hz, 3H).

10

EXAMPLE 56

This example illustrates the preparation of compound **56**.



To a solution of **56a** (117 mg, 0.32 mmol) in anhydrous THF (4 mL) was added trimethylsilyl isocyanate (0.24 mL, 1.6 mmol) and 4-dimethylaminopyridine (4 mg, 0.03 mmol). The reaction mixture was stirred at 65 °C under nitrogen atmosphere overnight. The mixture was concentrated *in vacuo*. The resulting residue was dissolved in anhydrous THF (4 mL), and to it was added tetrabutylammonium fluoride (0.7 mL, 1.0 M) in THF. The reaction mixture was stirred at room temperature overnight. The crude product was purified by column chromatography (60% ethyl acetate in hexane) to yield product **56** (95 mg, 72% over two steps). $^1\text{H-NMR}$ (DMSO-d_6): δ 10.20 (s, 1

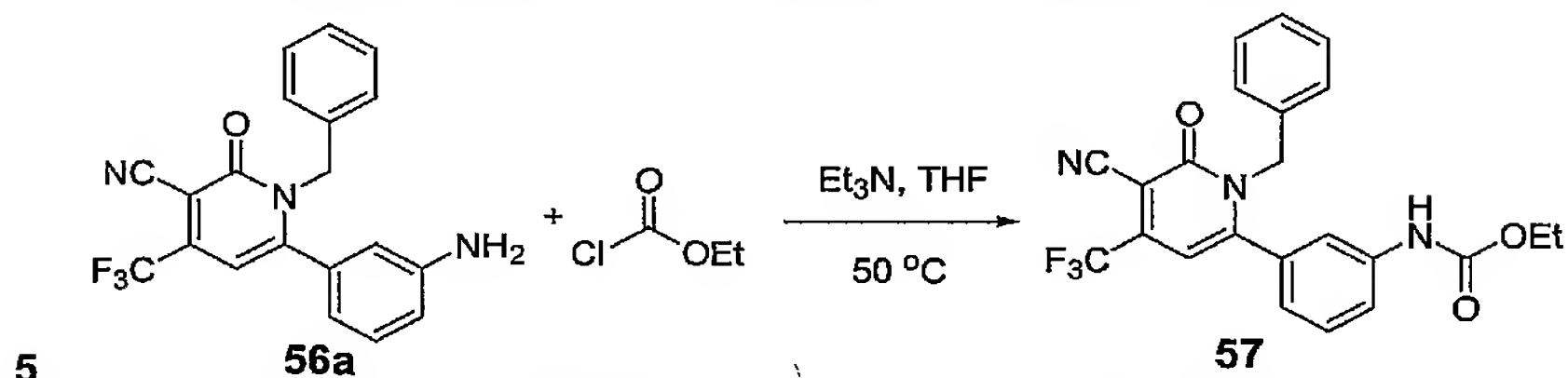
20

-318-

H), 9.04 (s, 1 H), 7.65 (m, 1 H), 7.58 (m, 1 H), 7.43 (m, 1 H), 7.29 (m, 3 H), 7.07 (m, 1 H), 7.02 (m, 2 H), 6.80 (s, 1 H), 5.23 (s, 2 H).

EXAMPLE 57

This example illustrates the preparation of compound **57**.

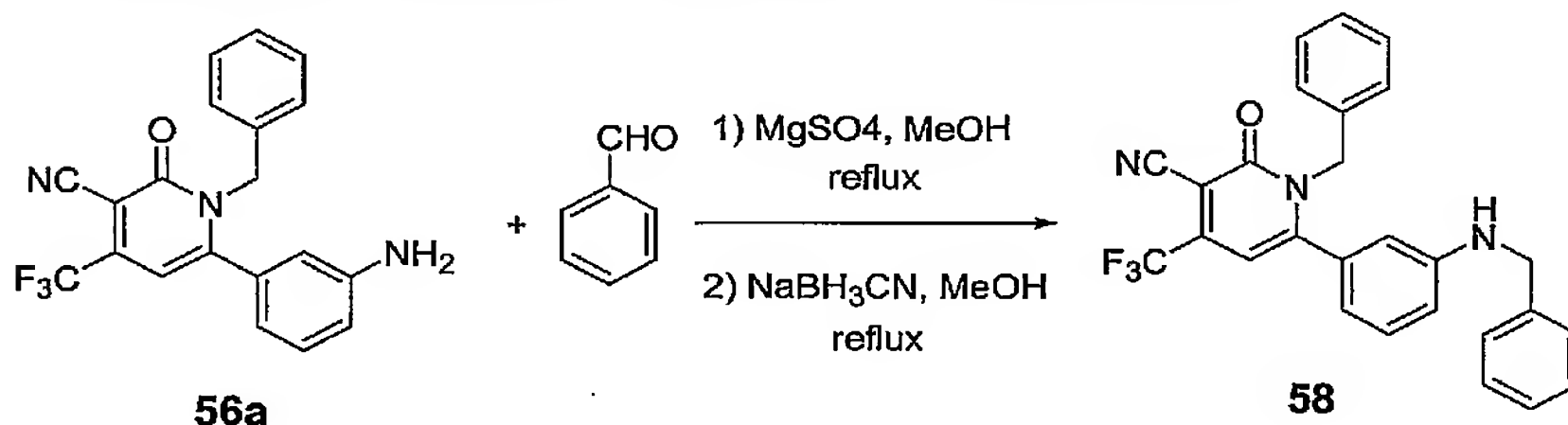


To a solution of **56a** (80 mg, 0.22 mmol) and triethyl amine (76 μL , 0.54 mmol) in anhydrous methylene chloride (2 mL) was added ethyl chloroformate (41 μL , 0.54 mmol). The reaction mixture was sealed in a vial and stirred at 50 $^{\circ}\text{C}$ overnight. The mixture was cooled off and concentrated *in vacuo*. The product was purified by column chromatography (40% ethyl acetate in hexane) to yield **57** (40 mg, 42% yield). $^1\text{H-NMR}$ (CDCl_3): δ 7.41 (m, 2 H), 7.34 (m, 1 H), 7.25-7.21 (m, 3 H), 6.91 (m, 2 H), 6.81 (m, 1 H), 6.64 (s, 1 H), 6.40 (s, 1 H), 5.27 (s, 2 H), 4.24 (q, 7.1 Hz, 2 H), 1.32 (t, 7.1 Hz, 3 H).

10

EXAMPLE 58

15 This example illustrates the preparation of compound **58**.



To a solution of **56a** (100 mg, 0.27 mmol) in methanol (15 mL) was added benzaldehyde (41 μL , 0.41 mmol) and anhydrous magnesium sulfate (500 mg). The reaction mixture was heated to reflux overnight. Sodium cyanoborohydride (85 mg, 1.36 mmol) was added to the mixture, which was

20

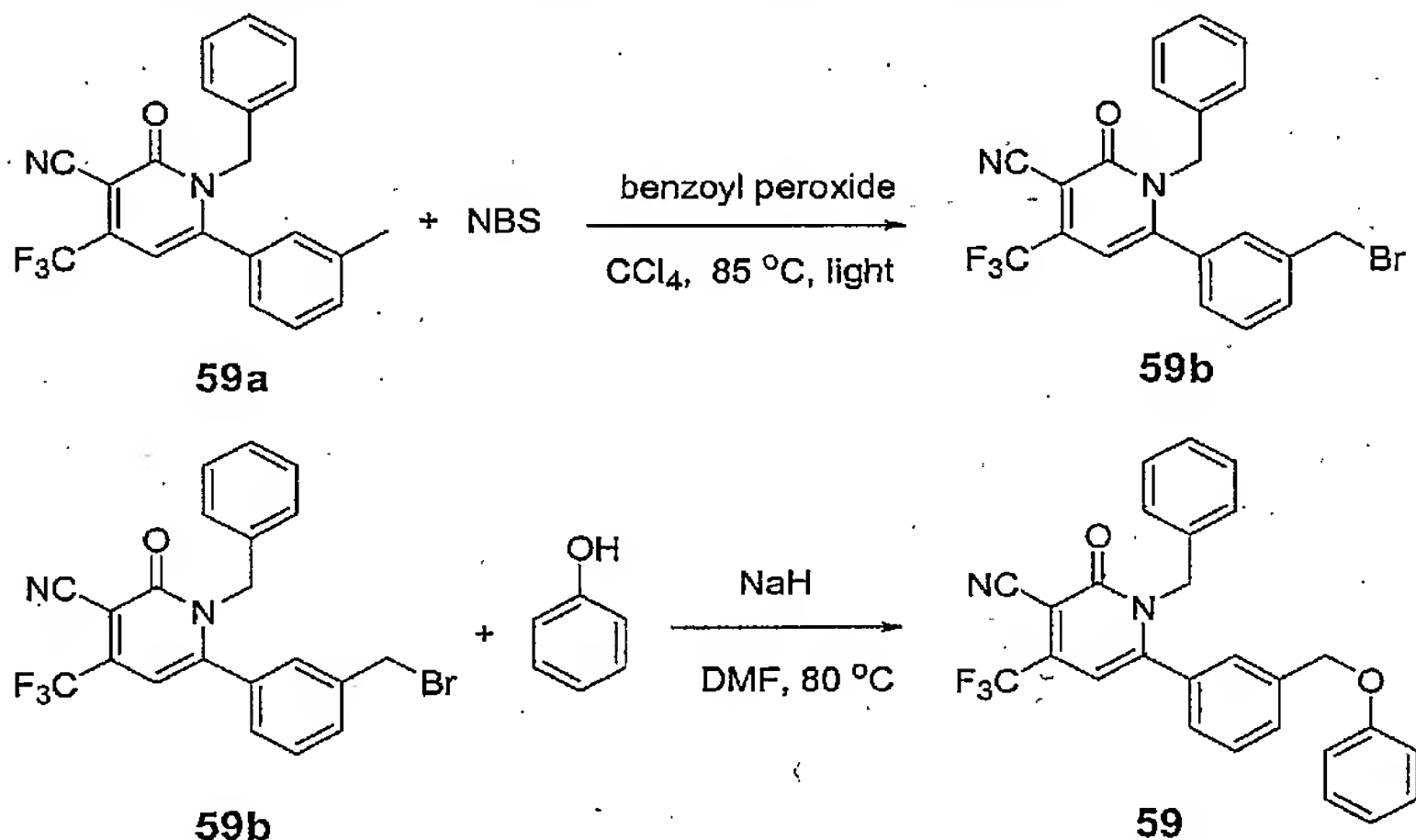
-319-

heated to reflux overnight. The reaction mixture was concentrated *in vacuo* and the crude mixture was partitioned between ethyl acetate and saturated sodium bicarbonate solution. The combined ethyl acetate was concentrated *in vacuo*. The crude product was purified by column chromatography (30% ethyl acetate in hexane) to yield compound **58** (24 mg, 19% yield).

¹H-NMR (CDCl₃): δ 7.38-7.19 (br, 10 H), 6.93 (m, 2 H), 6.75 (m, 1 H), 6.50 (m, 1 H), 6.38 (s, 1 H), 6.27 (s, 1 H), 5.19 (s, 2 H), 4.17 (s, 2 H).

EXAMPLE 59

This example illustrates the preparation of compound **59**.



10

A solution of **59a** (0.96 g, 2.61 mmol) in carbon tetrachloride (50 mL) was treated with N-bromosuccinimide (557 mg, 3.13 mmol) and catalytic amount of benzoyl peroxide. The reaction mixture was heated to reflux and irradiated with a 500 W floodlamp for 24 h. It was then cooled off and the white precipitate was filtered off. The solvent was evaporated to dryness, and the residue was purified by column chromatography (40% ethyl acetate in hexane) to yield **59b** (0.79 g, 65% yield). ¹H-NMR (CDCl₃): δ 7.56 (m, 1 H), 7.43 (m, 1 H), 7.25 (m, 3 H), 7.13 (m, 2 H), 6.88 (m, 2 H), 6.39 (s, 1 H), 5.24 (s, 2 H), 4.38 (s, 2 H).

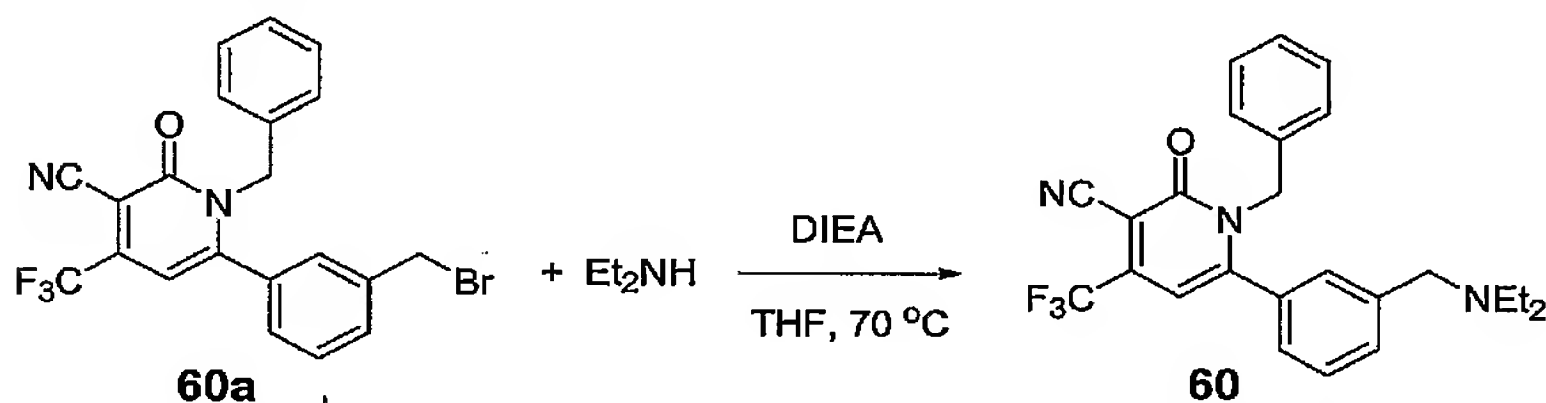
15

-320-

To a solution of **59b** (151 mg, 0.34 mmol) and phenol (127 mg, 1.35 mmol) in anhydrous DMF was added sodium hydride (54 mg, 60%, 1.35 mmol). The reaction mixture was stirred and heated to 80 °C for overnight. It was cooled off and poured into water and extracted with ether. The ether layer was dried with anhydrous sodium sulfate and concentrated *in vacuo*. The crude product was purified by column chromatography (15-30% ethyl acetate in hexane) to yield product **59** (66 mg, 42% yield). ¹H-NMR (CDCl₃): δ 7.60 (m, 1H), 7.46 (m, 1 H), 7.30 (m, 2 H), 7.24-7.20 (br, 4 H), 7.12 (m, 1 H), 7.00 (m, 1 H), 6.92 (m, 2 H), 6.86 (m, 2 H), 6.40 (s, 1 H), 5.22 (s, 1 H), 5.03 (s, 2 H).

EXAMPLE 60

This example illustrates the preparation of compound 60.

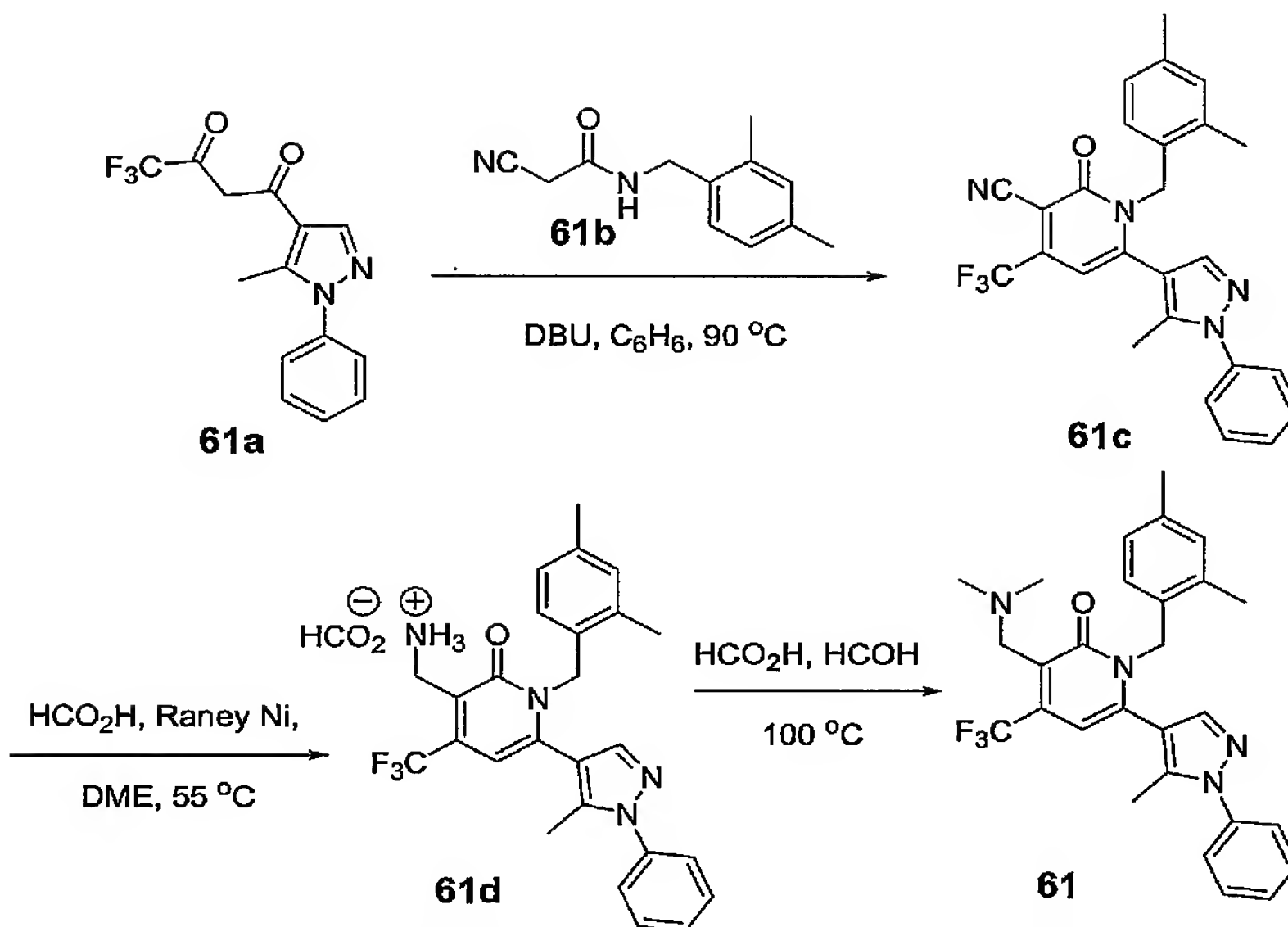


To a solution of **60a** (152 mg, 0.34 mmol) and diisopropylethyl amine (89 μ L, 0.51 mmol) in THF (2 mL) was added diethyl amine (53 μ L, 0.51 mmol). The reaction mixture was heated to 70 $^{\circ}$ C for overnight. The solvent was evaporated in vacuo and the crude product was purified by column chromatography (50% ethyl acetate in hexane) to yield product **60** (82 mg, 55%). $^1\text{H-NMR}$ (CDCl_3): δ 7.51 (m, 1 H), 7.38 (m, 1 H), 7.24-7.17 (m, 4 H), 7.07 (m, 1 H), 6.88 (m, 2 H), 6.41 (s, 1 H), 5.27 (s, 2 H), 3.52 (m, 2 H), 2.48 (m, 4 H), 1.01 (m, 6 H).

EXAMPLE 61

This example illustrates the preparation of compound **61**.

-321-



2,4-dimethylbenzyl cyanoacetamide **61a** (103 mg, 0.59 mmol) and diketone **61b** (175 mg, 0.59 mmol) were suspended in 2 mL of benzene. To the above reaction mixture was added DBU (45 μ L, 0.3 mmol). The mixture was sealed in a vial and stirred at 90 °C for overnight. The reaction mixture was concentrated *in vacuo* and the resulting residue was purified by column chromatography (35% ethyl acetate in hexane) to yield **61b** (50 mg, 18%). 1H -NMR ($CDCl_3$): δ 7.54-7.45 (m, 3 H), 7.34 (m, 3 H), 6.95 (m, 2 H), 6.61 (m, 1 H), 6.44 (s, 1 H), 5.28 (m, 2 H), 2.28 (s, 3 H), 2.08 (s, 3 H), 2.03 (s, 3 H).

1.0 g of aluminum-nickel catalyst was placed in 10 mL of 2 N aq NaOH and stirred in a flask cooled with ice water. The mixture was stirred for 45 min. The solution was decanted, while the solid Ni catalyst was kept washing with water 8 times until it became clear solution. The water was removed as much as possible, using a pipet. To a solution of **61b** (48 mg, 0.10 mmol) in 5 mL of DME was added 5 mL of formic acid. The reaction mixture was stirred at 55 °C for 4 h under a slow stream of nitrogen. The reaction mixture was filtered through a short pad of celite, and the celite was washed with MeOH. The

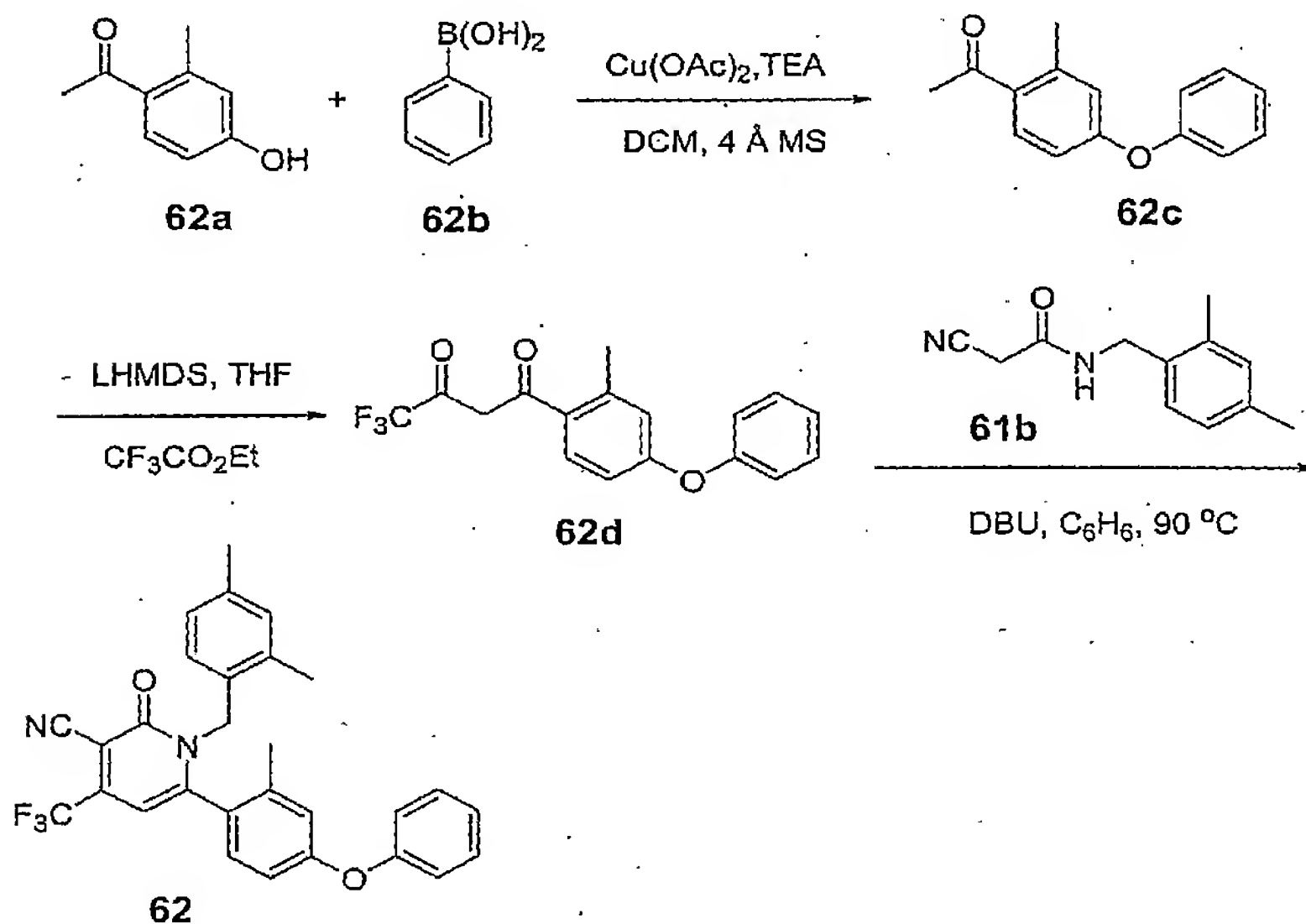
-322-

filtrate was concentrated *in vacuo*. The residue was purified by column chromatography (10% MeOH in DCM containing 0.1% triethyl amine) to provide product **61d** (26 mg, 50% yield).

The resulting product **61d** (21 mg, 0.04 mmol) was dissolved in a mixture of formic acid (2 mL, 96%) and formaldehyde (6 mL, 37% in water). The reaction mixture was heated at 100 °C for 16 h and then cooled off. The reaction mixture was neutralized by 10% aq NaOH with ice to weakly basic and then extracted with ether (3 x 20 mL). The combined ether was concentrated *in vacuo*. This crude product was purified by HPLC with 30% CH₃CN in water to yield **61** (12 mg, 80% yield) as trifluoroacetic acid salt. ¹H-NMR (CDCl₃): δ 7.50 (m, 2 H), 7.45 (m, 1 H), 7.36 (m, 3 H), 6.97 (s, 1 H), 6.91 (m, 1 H), 6.56 (m, 1 H), 6.49 (s, 1 H), 5.23 (s, 2 H), 4.34 (s, 2 H), 3.00 (s, 6 H), 2.27 (s, 3 H), 2.11 (s, 6 H). MS (ES⁺): 495.2 (M+H).

EXAMPLE 62

This example illustrates the preparation of compound **62**.



-323-

To a solution of 2-methyl-4-hydroxyacetophenone **62a** (0.5 g, 3.33 mmol) in anhydrous methylene chloride (30 mL) was added Cu(OAc)₂ (605 mg, 3.33 mmol), phenylboronic acid (812 mg, 6.66 mmol) and powdered 4 Å molecular sieves and triethylamine (2.32 mL, 16.65 mmol). The heterogeneous reaction mixture was stirred at ambient temperature for overnight. The resulting slurry was filtered through celite and the diaryl ether was isolated from the organic filtrate by column chromatography (30% ethyl acetate in hexane) to yield **62c** (590 mg, 78% yield). ¹H-NMR (CDCl₃): δ 7.73 (m, 1 H), 7.38 (m, 2 H), 7.19 (m, 1 H), 7.06 (m, 2 H), 6.82 (m, 2 H), 2.56 (s, 3 H), 2.53 (s, 3 H).

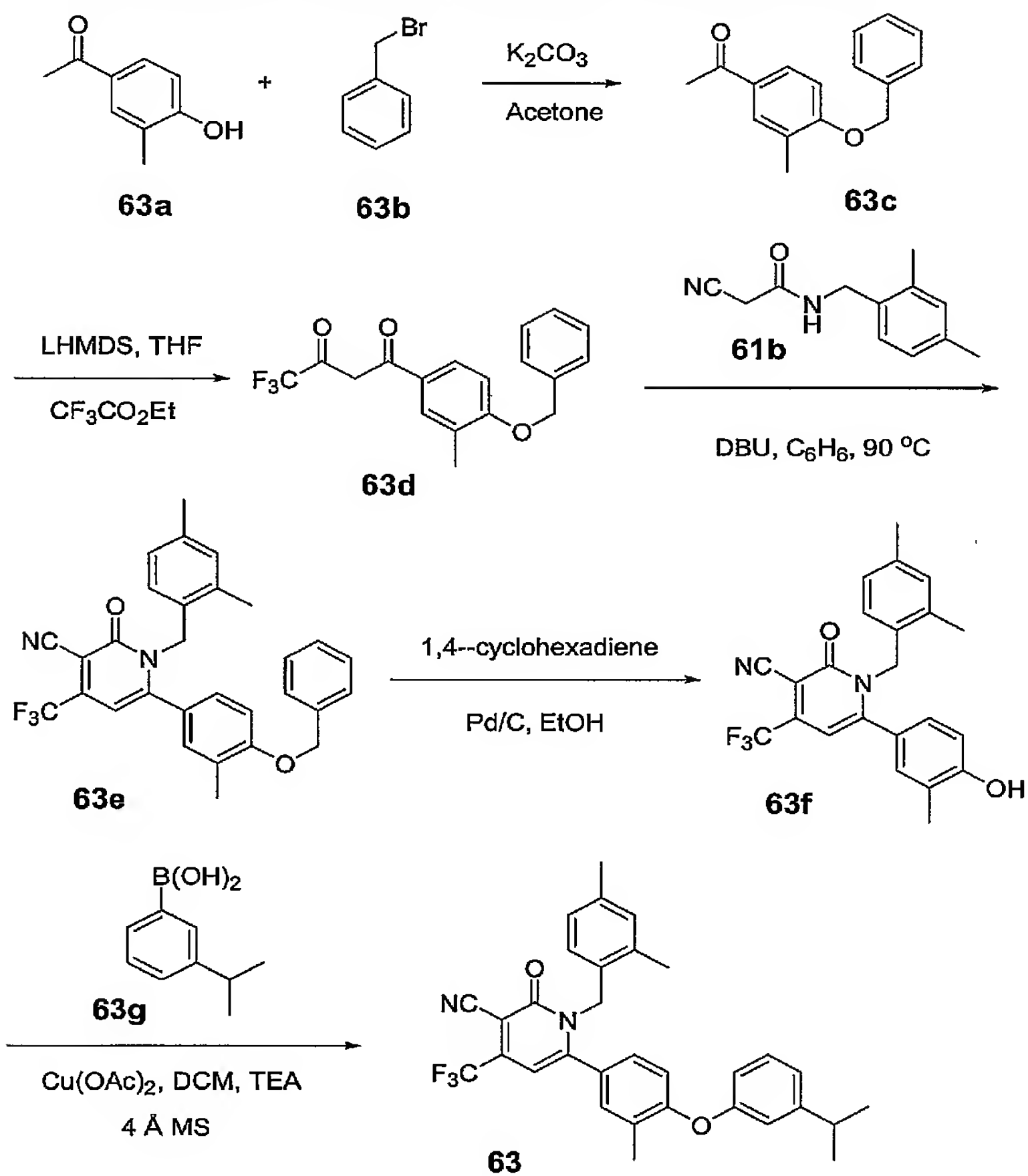
The diaryl ether **62c** (530 mg, 2.34 mmol) was dissolved in anhydrous THF (3 mL) and cooled to -78 °C under nitrogen atmosphere. A solution of lithium bis(trimethylsilyl)amide (2.4 mL, 1.0 M) in THF was added slowly. The reaction mixture was stirred at -20 °C under nitrogen atmosphere for 1 h. The reaction mixture was then cooled to -78 °C, and to it was added ethyl trifluoroacetate (417 µL, 3.5 mmol). The vigorously stirred solution was allowed to warm to ambient temperature overnight. The reaction mixture was poured into a mixture of 10% aq HCl and ice and extracted with chloroform three times. The chloroform extract was washed with water. The organic layer was separated and dried with anhydrous MgSO₄ and concentrated *in vacuo* to give crude product **62d** (1.05 g, 98% yield).

2,4-dimethylbenzyl cyanoacetamide **61b** (101 mg, 0.50 mmol) and diketone **62d** (161 mg, 0.50 mmol) were suspended in 2 mL of benzene. To the above reaction mixture was added DBU (40 µL, 0.25 mmol). The mixture was sealed in a vial and stirred at 90 °C for overnight. The reaction mixture was concentrated *in vacuo* and the resulting residue was purified by column chromatography (35% ethyl acetate in hexane) to yield product **62** (127 mg, 52% yield). ¹H-NMR (CDCl₃): δ 7.40 (m, 2 H), 7.20 (m, 1 H), 7.03 (m, 2 H), 6.84 (m, 4 H), 6.73 (m, 1 H), 6.60 (m, 1 H), 6.37 (s, 1 H), 5.31 (m, 1 H), 4.89 (m, 1 H), 2.73 (s, 3 H), 2.25 (s, 3 H), 1.92 (s, 3 H). MS (ES⁺): 489.2 (M+H).

EXAMPLE 63

-324-

This example illustrates the preparation of compound **63**.



-325-

To a solution of 3-methyl-4-hydroxyacetophenone **63a** (9.01 g, 60 mmol) and benzyl bromide **63b** (7.49 mL, 63 mmol) in acetone (120 mL) was added potassium carbonate (8.71 g, 63 mmol). The reaction mixture was stirred at
5 ambient temperature under nitrogen atmosphere for overnight. The white solid was filtered off and the solvent was concentrated *in vacuo* to yield product **63c** (14.13 g, 98% yield). The product was used for the next reaction without further purification.

The aryl benzyl ether **63c** (14.13 g, 59.3 mmol) was dissolved in anhydrous
10 THF (150 mL) and cooled to -78°C under nitrogen atmosphere. A solution of lithium bis(trimethylsilyl)amide (59.3 mL, 1.0 M) in THF was added slowly. The reaction mixture was stirred at -20°C under nitrogen atmosphere for 2 h. The reaction mixture was then cooled to -78°C , and to it was added ethyl trifluoroacetate (10.58 mL, 89 mmol). The vigorously stirred solution was
15 allowed to warm to ambient temperature overnight. The reaction mixture was poured into a mixture of 10% aq HCl and ice and extracted with chloroform three times. The chloroform extract was washed with water. The organic layer was separated and dried with anhydrous MgSO_4 and concentrated *in vacuo* to give crude product **63d** (19.5 g, 98% yield). The product was used
20 for the next reaction without purification.

2,4-dimethylbenzyl cyanoacetamide **61b** (3.01 g, 14.88 mmol) and diketone **63d** (5.0 g, 14.87 mmol) were suspended in 50 mL of benzene. To the above reaction mixture was added DBU (1.11 mL, 7.43 mmol). The mixture was heated to reflux under nitrogen atmosphere for overnight. The reaction
25 mixture was concentrated *in vacuo* and the resulting residue was purified by column chromatography (20% ethyl acetate in hexane) to yield product **63e** (3.90 g, 45% yield).

To a solution of **63e** (3.71 g, 7.38 mmol) in anhydrous ethanol (74 mL) was added 2.85 g of 10% Pd/C and 1,4-cyclohexadiene (6.98 mL, 73.8 mmol).
30 The mixture was stirred under nitrogen atmosphere for overnight. The solution

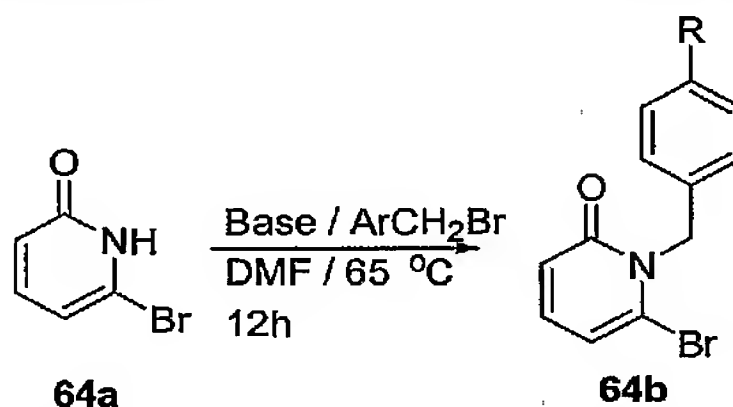
-326-

was filtered through a pad of celite and the solvent was concentrated in vacuo to yield product **63f** (2.96 g, 97%).

To a solution of **63f** (103 mg, 0.25 mmol) in anhydrous methylene chloride (3 mL) was added Cu(OAc)₂ (91 mg, 0.5 mmol), 3-isopropylphenylboronic acid (82 mg, 0.5 mmol) and powdered 4 Å molecular sieves and triethylamine (174 µL, 1.25 mmol). The heterogeneous reaction mixture was stirred at ambient temperature for overnight. The resulting slurry was filtered through celite and the diaryl ether was isolated from the organic filtrate by column chromatography (20% ethyl acetate in hexane) to yield **63** (63 mg, 47% yield). ¹H-NMR (CDCl₃): δ 7.27 (m, 1 H), 7.03 (m, 1 H), 6.98-6.85 (m, 5 H), 6.74 (m, 2 H), 6.64 (m, 1 H), 6.46 (s, 1 H), 5.15 (s, 2 H), 2.90 (hep, J = 7.0 Hz, 1 H), 2.27 (s, 3 H), 2.21 (s, 3 H), 1.99 (s, 3 H), 1.25 (d, J = 7.0 Hz, 6 H). MS (ES⁺): 531.3 (M+H).

EXAMPLE 64

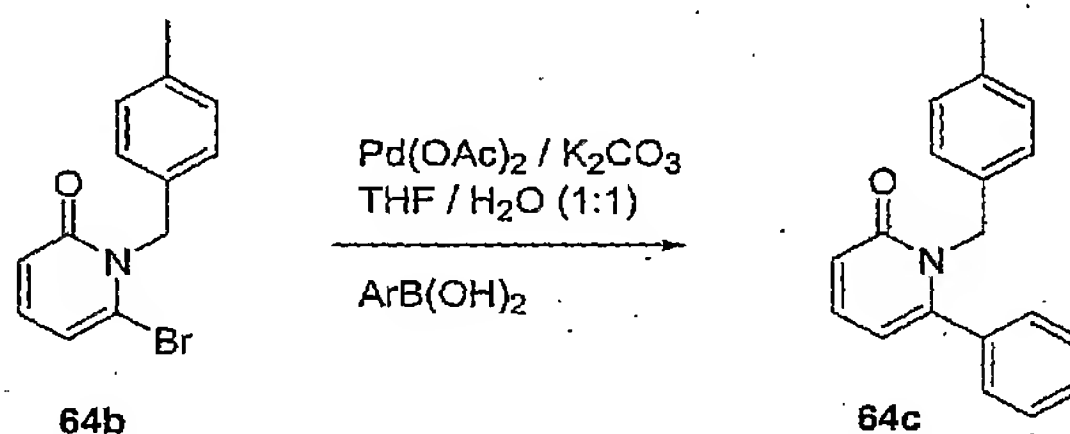
This example illustrates the preparation of compound **64**.



Method A (R = Me): To a solution of bromopyridone **64a** (2.12 g, 12.2 mmols) in 60 mL of DMF at room temperature was added LiH (145.0 mg, 18.3 mmols). After stirring for 1 hour at 65 °C, 4-methylbenzyl bromide (2.7 g, 14.6 mmols) was added and heating continued for 12 h. The solution was cooled to room temperature and concentrated under reduced pressure. Pyridone **64b** (R = Me) was isolated from the residue by column chromatography on silica gel (0 to 20% EtOAC / hexanes) as a colorless oil (1.6 g, 47%). ¹H NMR (CDCl₃) δ: 7.34 (t, J = 7.8 Hz, 1H), 7.28 (d, J = 8.0 Hz, 2H), 7.12 (d, J = 8.0 Hz, 2H), 6.98 (d, J = 7.6 Hz, 1H), 6.64 (d, J = 8.0 Hz, 1H), 5.24 (s, 2H), 2.29 (s, 3H).

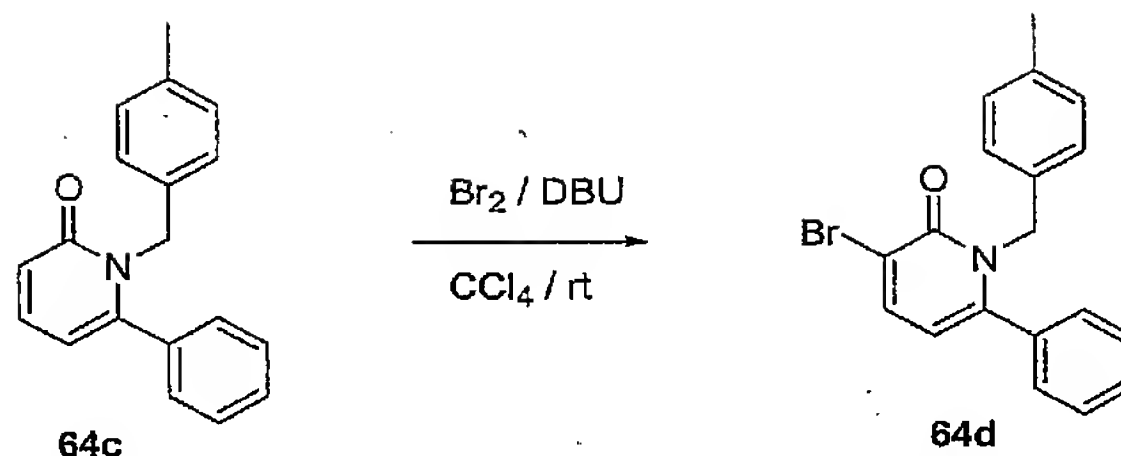
-327-

Method B (R = H): To a solution of bromopyridone (405.0 mg, 2.3 mmols) in 6.0 mL of DME:DMF (10:1, v/v) at 0 °C was added NaH (92.0 mg, 2.3 mmols, 60% dispersion in mineral oil). After 10 minutes LiBr (800.0 mg, 9.2 mmols) was added and the mixture warmed to room temperature over 15 minutes and then benzyl bromide (786.6 mg, 4.6 mmols) was added. The resulting solution was heated to 65 °C for 12h, cooled to room temperature, diluted with saturated aqueous sodium chloride solution, and extracted with EtOAc. The combined organic layers were dried over MgSO₄ and concentrated under reduced pressure. Pyridone (R = H) was isolated from the residue by column chromatography on silica gel (0 to 20% EtOAc / hexanes) as a colorless oil (533 mg, 88%). ¹H NMR (CDCl₃) δ: 7.40-4.24 (m, 6H), 7.00 (d, J = 7.2 Hz, 1H), 6.66 (d, J = 7.6 Hz, 1H), 5.28 (s, 2H).

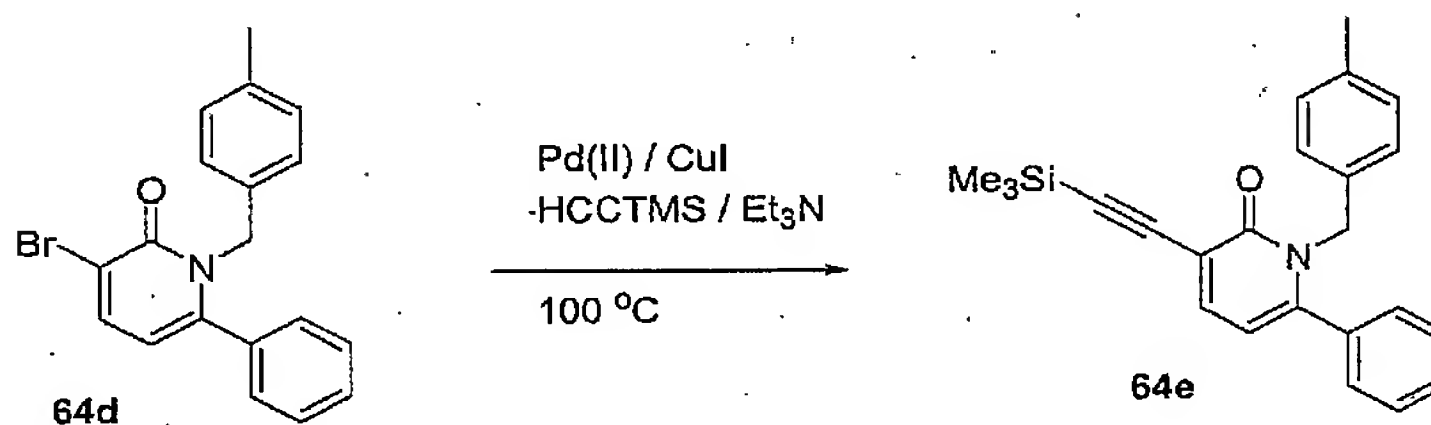


A degassed solution of bromopyridone **64b** (100 mg, 0.4 mmol) and phenylboronic acid (44 mg, 0.4 mmol) in 0.9 mL THF was added Pd(OAc)₂ (4 mg, 0.02 mmol). A degassed solution of Na₂CO₃ (95 mg, 0.9 mmol) in 0.9 mL H₂O was added and the resulting mixture heated to reflux for 12 h. The mixture was cooled to room temperature, diluted with H₂O, and extracted with EtOAc. The combined organic layers were dried over NaSO₄ before being concentrated under reduced pressure. The product **64c** (91 mg, 97%) was isolated as a colorless solid from the residual oil by column chromatography on silica (0 to 20% EtOAc / hexanes). ¹H NMR (CDCl₃) δ: 7.52 (dd, J = 8.6, 1.6 Hz, 1H), 7.39-7.26 (7H), 7.11 (d, J = 8.0 Hz, 2H), 6.98 (d, J = 7.2 Hz, 1H), 6.64 (d, J = 8.1 Hz, 1H), 5.24 (s, 2H), 2.29 (s, 3H).

-328-



To a solution of pyridone **64c** (70 mg, 0.3 mmol) in 0.54 mL CCl_4 at 0 °C in the dark (foil wrapped flask) was added Br_2 (62 mg, 0.4 mmol) and DBU (61 mg, 0.4 mmol). The resulting solution was allowed to warm to slowly room temperature and stir for 12 h. The solution was diluted with CH_2Cl_2 (25 mL) and washed with 1N aqueous HCl, saturated aqueous NaHCO_3 , and dried over Na_2SO_4 before being concentrated under reduced pressure. The product **64d** (71 mg, 75%) was isolated from the residual oil as a colorless solid by column chromatography on silica (0 to 5% EtOAc / hexanes). ^1H NMR (CDCl_3) δ : 7.92 (m, 2H), 7.78 (d, $J = 8.0$ Hz, 1H), 7.37 (m, 5H), 7.17 (d, $J = 8.0$ Hz, 1H), 7.12 (d, $J = 8.0$ Hz, 2H), 5.48 (s, 2H), 2.28 (s, 3H).



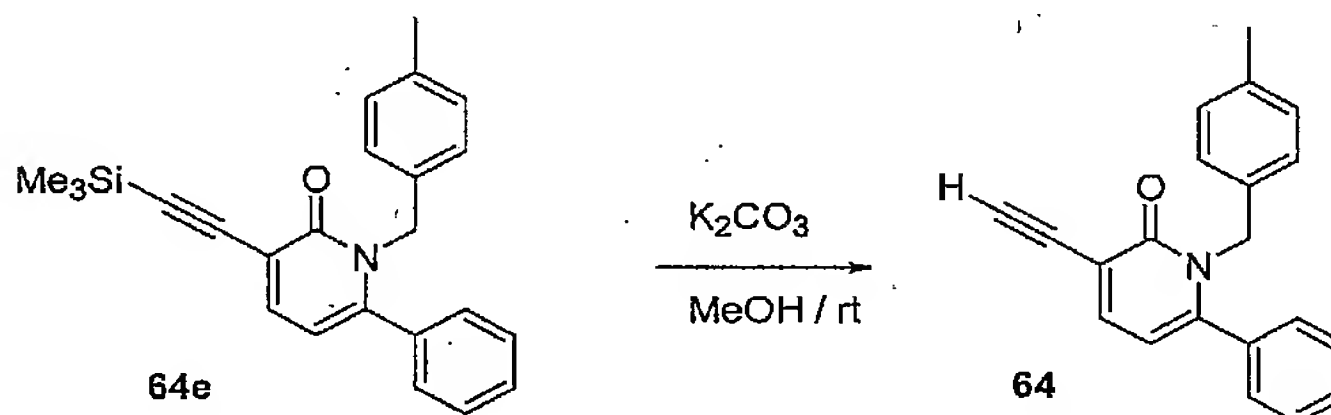
15

To a solution of bromide **64d** (12 mg, 0.03 mmol) in 0.3 mL Et_3N was added CuI (2 mg, 0.01 mmol), dichloro(bis-triphenylphosphine)palladium (II) (4 mg, 0.005 mmol), and 1,3-(bis-diphenylphosphino)propane (2 mg, 0.005). The system was purged with N_2 , trimethylsilylacetylene (59 mg, 0.6 mmol) added and the resulting mixture heated to 100 °C for 17 h. Upon cooling to room temperature the mixture was concentrated under reduced pressure and

20

-329-

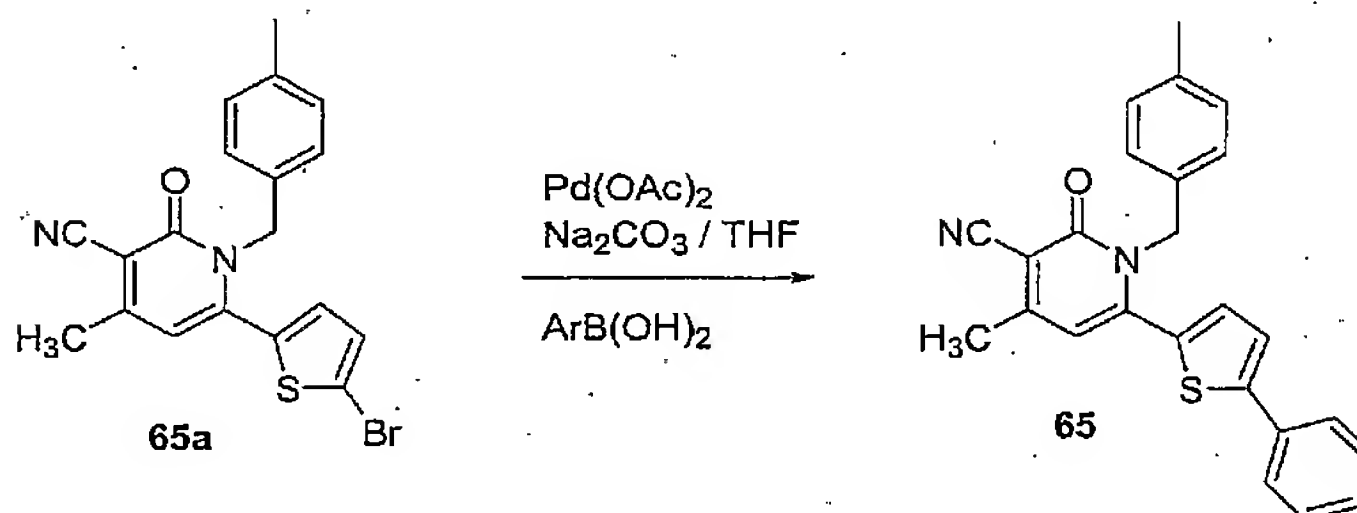
product **64e** (8 mg, 73%) was isolated from the residual oil as a yellow oil by column chromatography on silica (0 to 5% EtOAc / hexanes). ¹H NMR (CDCl₃) δ: 8.09 (d, J = 7.2 Hz, 1H), 7.82 (d, J = 7.6 Hz, 1H), 7.70-7.37 (m, 5H), 7.39 (d, J = 7.6 Hz, 2H), 7.34 (d, J = 8.0 Hz, 2H), 5.62 (s, 2H), 2.42 (s, 3H), 0.34 (s, 9H).



Alkyne **64e** (2 mg, 0.005 mmol) was combined with K₂CO₃ (3 mg, 0.025 mmol) in 0.1 mL of MeOH and stirred overnight at room temperature. The mixture was concentrated under reduced pressure and product **64** (1 mg) was isolated from the residual oil as a yellow oil by column chromatography on silica (0 to 5% EtOAc / hexanes). ¹H NMR (CDCl₃) δ: 7.95 (d, J = 8.4 Hz, 1H), 7.72 (d, J = 8.0 Hz, 1H), 7.39 (m, 5H), 7.26 (d, J = 8.0 Hz, 2H), 7.10 (d, J = 8.0 Hz, 2H), 5.51 (s, 2H), 3.30 (s, 1H), 2.28 (s, 3H).

Example 65

This example illustrates the preparation of compound **65**.

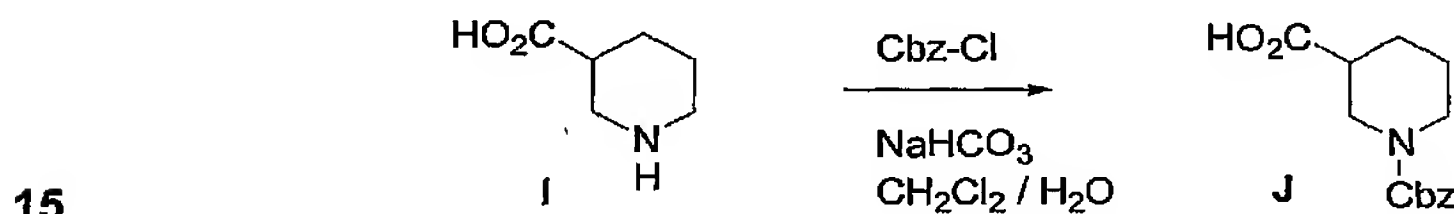


-330-

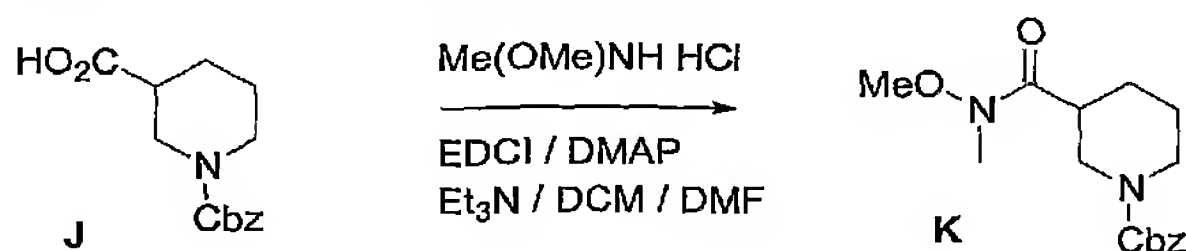
To a degassed solution of thienylbromide **65a** (50 mg, 0.11 mmol) and phenylboronic acid (13 mg, 0.11 mmol) in 0.6 mL THF was added Pd(OAc)₂ (1 mg, 0.006 mmol). A degassed solution of Na₂CO₃ (30 mg, 0.3 mmol) in 0.6 mL H₂O was added and the resulting mixture heated to reflux for 12 h. The mixture was cooled to room temperature, diluted with H₂O and extracted with EtOAc. The combined organic layers were dried over NaSO₄ before being concentrated under reduced pressure. The product **65** (28 mg, 55%) was isolated as a colorless solid from the residual oil by column chromatography on silica (10 to 20% EtOAc / hexanes). ¹H NMR (CDCl₃) δ: 7.51 (d, J = 8.0 Hz, 2H), 7.35 (m, 5H), 7.35 (d, J = 7.3 Hz, 1H), 7.01 (d, J = 3.8 Hz, 1H), 6.88 (d, J = 8.1 Hz, 2H), 6.56 (s, 1H), 5.38 (s, 2H), 2.25 (s, 3H).

Example 66

This example illustrates the preparation of compound **66**.

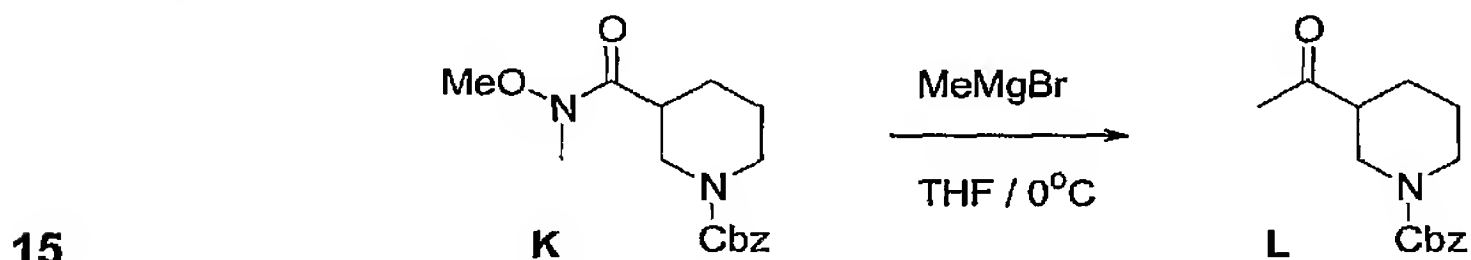


To a solution of acid **I** (2.0 g, 15.5 mmols) in 8.0 mL of dioxane was added benzyl chloroformate (3.1 g, 18.6 mmols) at room temperature followed by the addition of 8 mL of saturated aqueous NaHCO₃. The resulting mixture was vigorously stirred for 4 hours, the dioxane removed under reduced pressure, and the resulting solution diluted with H₂O. Extraction with CH₂Cl₂ was followed by drying the combined fractions over Na₂SO₄ and concentration under reduced pressure. The product **J** (3.3 g, 81%) was isolated as a colorless oil from the residual oil by column chromatography on silica (5-10% MeOH / CH₂Cl₂). ¹H NMR (CDCl₃) δ: 7.36 (m, 5H), 5.13 (m, 2H), 4.19 (bm, 1H), 3.97 (m, 1H), 3.13 (bm, 1H), 2.94 (ddd, J = 3.0, 10.6, 13.6 Hz, 1H), 2.53 (bm, 1H), 2.09 (m, 1H), 1.72 (m, 2H), 1.51 (bm, 1H).

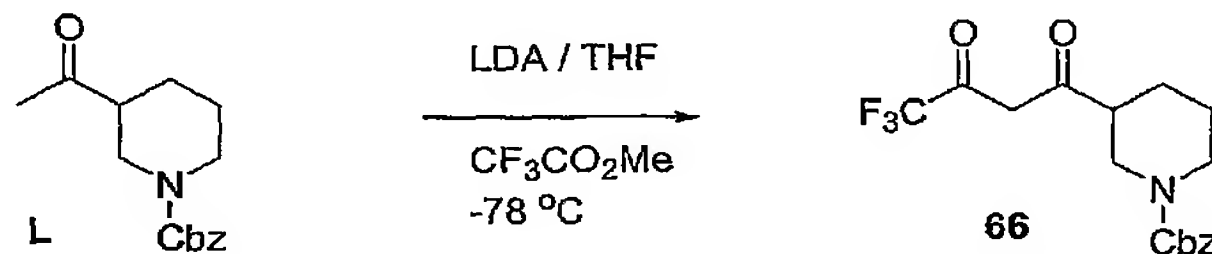


-331-

To a solution of acid **J** (3.3 g, 12.6 mmols) in 120 mL CH₂Cl₂:DMF (4:1, v/v) was added 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDCI) (4.8 g, 25.2 mmols) and 4-*N,N*-dimethylaminopyridine (77 mg, 0.6 mmol). After stirring for 30 minutes *N,O*-dimethylhydroxylamine hydrochloride (1.2 g, 12.6 mmols) followed by triethylamine (1.3 g, 12.6 mmols). After stirring for 12 hours the solution was concentrated under reduced pressure and the residue dissolved in CH₂Cl₂ (200 mL). The solution was then washed with H₂O and 1N aqueous HCl before being dried over Na₂SO₄ and concentrated under reduced pressure. The product **K** (3.2 g, 81%) was isolated as a pale yellow oil from the residual oil by column chromatography on silica (5-10% MeOH / CH₂Cl₂). ¹H NMR (CDCl₃) δ: 7.35 (m, 5H), 5.13 (m, 2H), 4.20 (bm, 1H), 4.11 (m, 1H), 3.72 (s, 3H), 3.59 (s, 3H), 2.92 (m, 1H), 2.81 (m, 1H), 2.19 (m, 1H), 1.94 (m, 1H), 1.70 (m, 2H), 1.51 (m, 1H).



To a solution of amide **K** (600 mg, 2.0 mmols) in THF (20 mL) at 0 °C was added MeMgBr (1.2 mL, 2.2 mmols, 1.4 M in THF). After stirring for 1 hour, the reaction was quenched at 0 °C by the addition of 1N HCl in EtOH. The solution was diluted with CH₂Cl₂:Et₂O (100 ml, v/v) and washed with saturated aqueous NaCl before being dried (Na₂SO₄) and concentrated under reduced pressure. The product **L** (257 mg, 50%) was isolated as a colorless oil from the residual oil by column chromatography on silica (10-50% EtOAc / hexanes). ¹H NMR (CDCl₃) δ: 7.37 (m, 5H), 5.15 (m, 2H), 4.22 (bm, 1H), 4.04 (bm, 1H), 3.02 (m, 1H), 2.88 (bm, 1H), 2.54 (bm, 1H), 2.19 (s, 3H), 2.04 (bm, 1H), 1.76 (m, 1H), 1.55 (m, 2H).

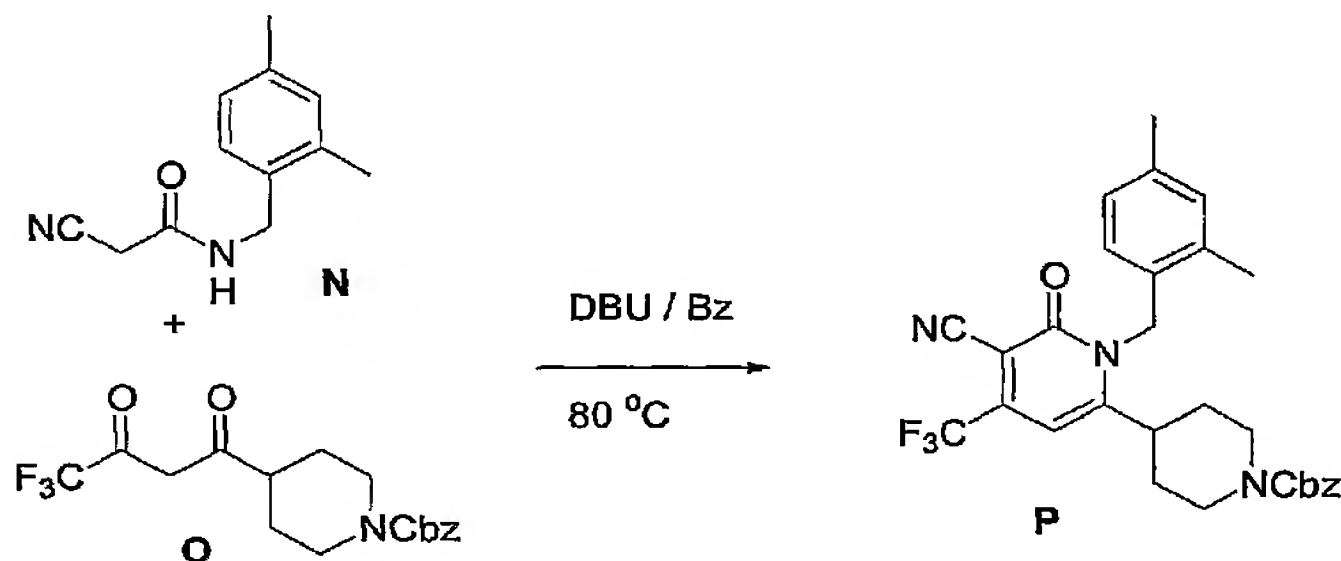


-332-

To a solution of ketone L (237 mg, 0.9 mmol) in 3.0 mL THF at -78 °C was added a solution of lithium diisopropylamide (0.45 mL, 0.9 mmol, 2.0M in THF). After stirring for 5 minutes ethyl trifluoromethylacetate (155 mg, 1.1 mmols) was added. Stirring for 2 hours at -78 °C was followed by warming to room temperature and the addition of EtOAc (50 mL). The resulting solution was washed with 10% aqueous H₂SO₄ and H₂O before being dried with Na₂SO₄ and concentrated under reduced pressure. The product **66** (50 mg, 16%) was isolated from the residual oil by column chromatography on silica (10-50% EtOAc / hexanes). ¹H NMR (CDCl₃) δ: 7.34 (m, 5H), 5.96 (s, 1H), 5.14 (m, 2H), 4.18 (bm, 1H), 4.07 (m, 1H), 3.01 (m, 1H), 2.89 (m, 1H), 2.68 (m, 1H), 2.52 (bm, 1H), 2.28 (m, 1H), 1.73 (m, 2H).

Example 67

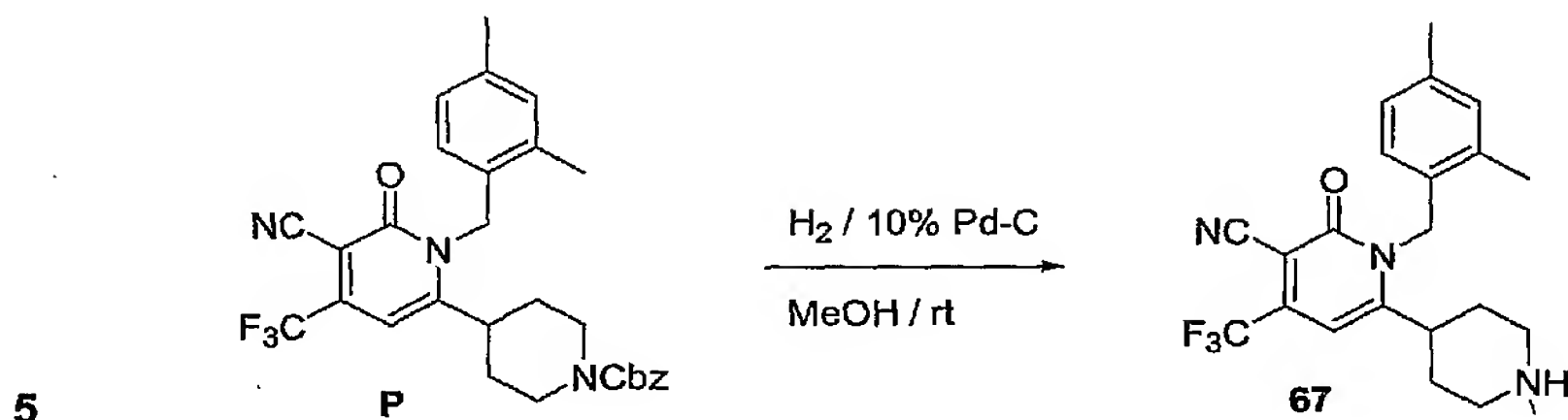
This example illustrates the preparation of compound **67**.



A solution of amide **N** (81 mg, 0.4 mmol), diketone **O** (150 mg, 0.4 mmol), and DBU (30.4 mg, 0.2 mmol) in 2.0 mL benzene was heated to reflux for 12 hours. The solution was cooled to room temperature and concentrated under reduced pressure. The product **P** (118 mg, 58%) was isolated as a pale yellow solid from the residue by column chromatography on silica (10-50% EtOAc / hexanes). ¹H NMR (CDCl₃) δ: 7.34 (m, 5H), 7.10 (d, J = 8.1 Hz, 1H), 7.01 (t, J = 13.4 Hz), 6.93 (d, J = 8.0 Hz), 6.35 (s, 1H), 5.35 (s, 2H), 5.10

-333-

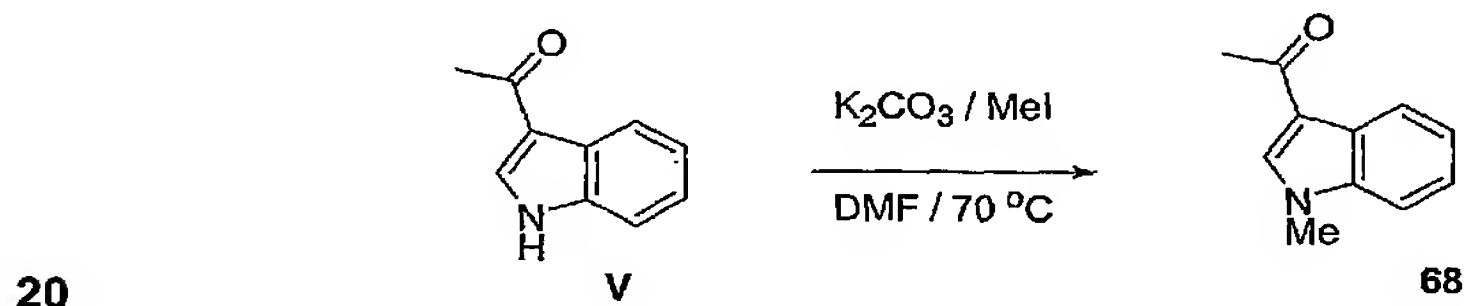
(s, 2H), 4.27 (bm, 2H), 2.68 (m, 1H), 2.60 (bm, 2H), 2.30 (s, 3H), 2.28 (s, 3H), 1.63 (m, 2H), 1.57 (m, 2H).



To a solution of pyridone **P** (50 mg, 0.1 mmol) in 0.5 mL MeOH was added 10% Pd-C (5 mg, 10 wt%). The mixture was then stirred under H₂ (1 atm) at room temperature for 30 minutes. The flask was purged with N₂ and the mixture filtered through a pad of Celite using an EtOAc wash. The filtrate was concentrated under reduced pressure and the product **67** (20 mg, 51%) was isolated from the residual oil by column chromatography on silica (5-20% MeOH / CH₂Cl₂). ¹H NMR (CDCl₃) δ: 7.10 (d, J = 7.6 Hz, 1H), 7.01 (t, J = 14.6 Hz, 1H), 6.93 (d, J = 7.3 Hz, 1H), 6.35 (s, 1H), 5.34 (m, 2H), 4.26 (bm, 2H), 2.65 (m, 1H), 2.51 (m, 2H), 2.30 (s, 3H), 2.28 (s, 3H), 1.66 (m, 2H).

Example 68

This example illustrates the preparation of compound **68**.



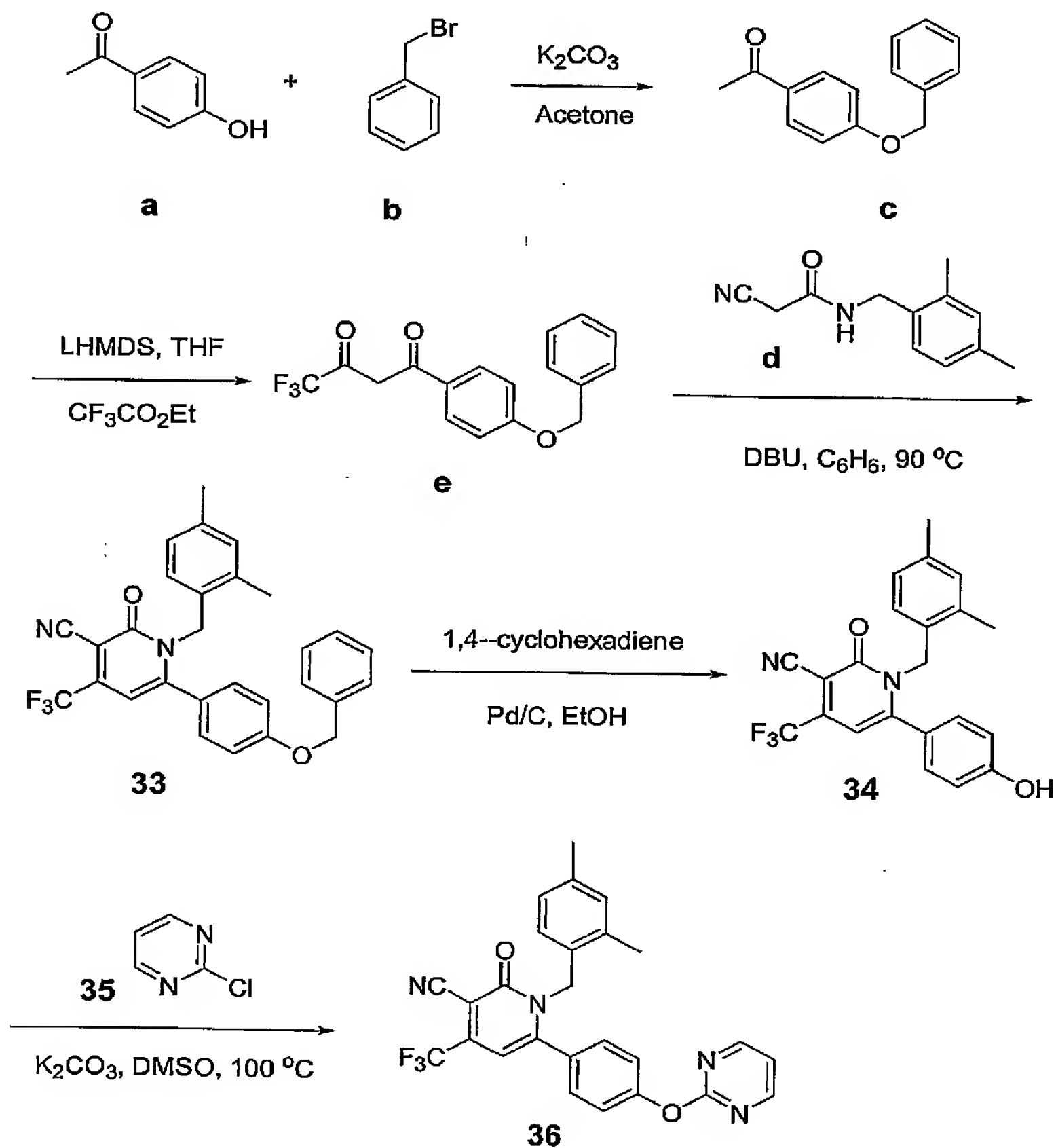
To a solution of indole **V** (0.5 g, 3.1 mmols) in 10 mL DMF was added MeI (483 mg, 3.4 mmols) and K₂CO₃ (1.3 g, 9.3 mmols). The resulting

-334-

mixture was heated to 70 °C for 15 hours, cooled to room temperature, and concentrated under reduced pressure. The product **68** (569 mg, 99%) was isolated as an off-white solid from the residual oil by column chromatography on silica (5-10% MeOH / CH₂Cl₂). ¹H NMR (CDCl₃) δ : 8.12 (m, 1H), 7.27 (s, 1H), 7.05-6.92 (m, 3H), 3.38 (s, 3H), 2.16 (s, 3H).

Example 69

This example illustrates the preparation of compound **69**.



-335-

To a solution of 4-hydroxyacetophenone **30** (6.81 g, 50 mmol) and benzyl bromide **23** (5.95 mL, 50 mmol) in acetone (100 mL) was added potassium carbonate (7.6 g, 55 mmol). The reaction mixture was stirred at ambient temperature under nitrogen atmosphere for overnight. The white solid was
5 filtered off and the solvent was concentrated *in vacuo* to yield product **31** (11.8 g, 98% yield). The product was used for the next reaction without further purification.

The aryl benzyl ether **31** (11.14 g, 49.2 mmol) was dissolved in anhydrous THF (70 mL) and cooled to -78°C under nitrogen atmosphere. A solution of
10 lithium bis(trimethylsilyl)amide (49.2 mL, 1.0 M) in THF was added slowly. The reaction mixture was stirred at -20°C under nitrogen atmosphere for 2 h. The reaction mixture was then cooled to -78°C , and to it was added ethyl trifluoroacetate (8.78 mL, 73.8 mmol). The vigorously stirred solution was allowed to warm to ambient temperature overnight. The reaction mixture was
15 poured into a mixture of 10% aq HCl and ice and extracted with chloroform three times. The chloroform extract was washed with water. The organic layer was separated and dried with anhydrous MgSO_4 and concentrated *in vacuo* to give crude product **32** (15.5 g, 98% yield). The product was used for the next reaction without purification.

20 2,4-dimethylbenzyl cyanoacetamide **13** (2.02 g, 10 mmol) and diketone **32** (3.22 g, 10 mmol) were suspended in 25 mL of benzene. To the above reaction mixture was added DBU (0.75 mL, 5.0 mmol). The mixture was heated to reflux under nitrogen atmosphere for overnight. The reaction mixture was concentrated *in vacuo* and the resulting residue was purified by
25 column chromatography (20% ethyl acetate in hexane) to yield product **33** (3.2 g, 66% yield).

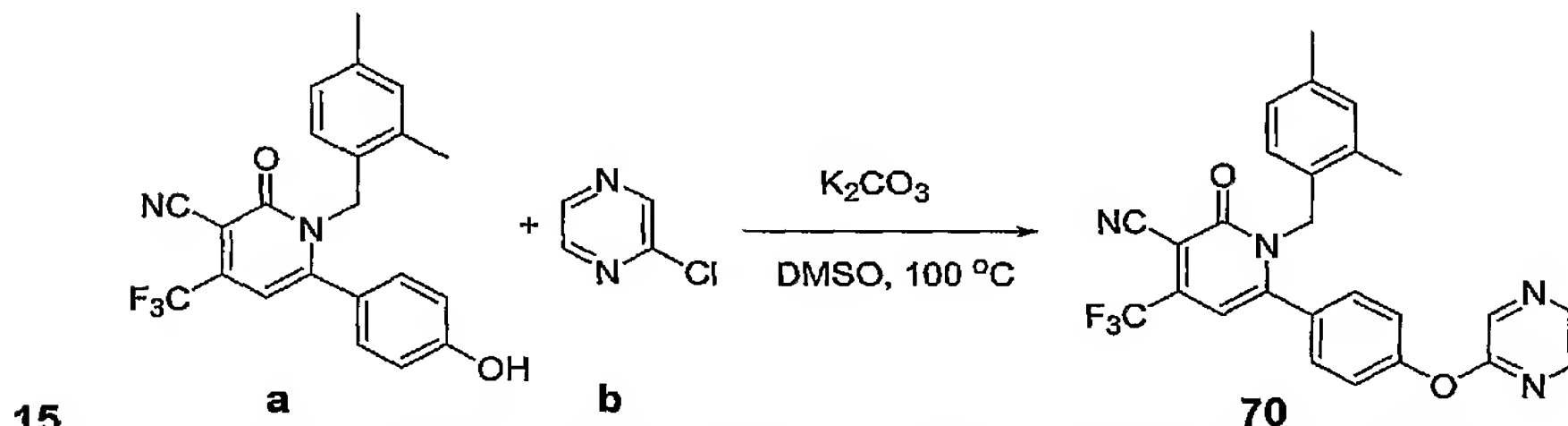
To a solution of **33** (2.84 g, 5.81 mmol) in anhydrous ethanol (90 mL) was added 2.85 g of 10% Pd/C and 1,4-cyclohexadiene (5.5 mL, 58.1 mmol). The mixture was stirred under nitrogen atmosphere for overnight. The solution was
30 filtered through a pad of celite and the solvent was concentrated *in vacuo* to yield product **34** (2.20 g, 95%).

-336-

To a solution of **34** (100 mg, 0.25 mmol) and 2-chloropyrimidine **35** (29 mg, 0.25 mmol) in DMSO (2 mL) was added potassium carbonate (52 mg, 0.38 mmol). The reaction mixture in a sealed vial was stirred and heated to 100 °C overnight. After cooling off, the mixture was poured into water and extracted with chloroform. The chloroform extract was dried with anhydrous MgSO₄ and concentrated in vacuo. The crude product was purified by column chromatography (30 –60% EtOAc in hexane) to yield the product **36** (65 mg, 55% yield). ¹H-NMR (CDCl₃): δ8.58 (d, J = 4.8 Hz, 2H), 7.21 (m, 3 H), 7.12 (m, 1 H), 6.95 (m, 1 H), 6.91 (s, 1 H), 6.63 (m, 1 H), 6.50 (s, 1 H), 5.15 (s, 2 H), 2.27 (s, 3 H), 1.97 (s, 3 H). MS (ES⁺): 477.1 (M+H).

Example 70

This example illustrates the preparation of compound **70**.



To a solution of **a** (71 mg, 0.18 mmol) and 2-chloropyrazine **b** (20 mg, 0.18 mmol) in DMSO (2 mL) was added potassium carbonate (37 mg, 0.27 mmol). The reaction mixture in a sealed vial was stirred and heated to 100 °C overnight. After cooling off, the mixture was poured into water and extracted with chloroform. The chloroform extract was dried with anhydrous MgSO₄ and concentrated in vacuo. The crude product was purified by column chromatography (25 –50% EtOAc in hexane) to yield the product **70** (48 mg, 57% yield). ¹H-NMR (CDCl₃): δ8.49 (m, 1 H), 8.34 (m, 1 H), 8.11(m, 1 H), 7.19 (m, 4 H), 6.95 (m, 1 H), 6.92 (m, 1 H), 6.63 (m, 1 H), 6.49 (s, 1 H), 5.15 (s, 2 H), 2.28 (s, 3 H), 1.98 (s, 3 H). MS (ES⁺): 477.2 (M+H).

Example 71

-337-

FRET Coactivator assay

The FRET coactivator assay measures the ability of LXR ligands to promote protein-protein interactions between the ligand binding domain (LBD) of LXR and transcriptional coactivator proteins. The assay involves the use a recombinant Glutathione-S-transferase (GST)-nuclear receptor ligand binding domain (LBD) fusion protein and a synthetic biotinylated peptide sequence derived from the receptor interacting domain of a co-activator peptide such as the steroid receptor coactivator 1 (SRC-1). Typically GST-LBD is labeled with a europium chelate (donor) via a europium-tagged anti-GST antibody, and the coactivator peptide is labeled with allophycocyanin via a streptavidin-biotin linkage.

In the presence of an agonist for the nuclear receptor, the peptide is recruited to the GST-LBD bringing europium and allophycocyanin into close proximity to enable energy transfer from the europium chelate to the allophycocyanin. Upon excitation of the complex with light at 340 nm excitation energy absorbed by the europium chelate is transmitted to the allophycocyanin moiety resulting in emission at 665 nm. If the europium chelate is not brought in to close proximity to the allophycocyanin moiety there is little or no energy transfer and excitation of the europium chelate results in emission at 615 nm. Thus the intensity of light emitted at 665 nm gives an indication of the strength of the protein-protein interaction.

A. Required Materials:

1. Partially purified recombinant protein comprising glutathione-S-transferase fused in frame to the LXR-ligand binding domain (comprising amino acids 188-447 of human LXR α , or amino acids 198-461 of human LXR β).
2. Biotinylated peptide containing a SRC-1 LXXLL receptor interaction motif (B-SRC-1)

-338-

3. Anti-GST antibody conjugated to an Europium chelate (α GST-K) (From Wallac/PE Life Sciences Cat# AD0064)
4. Streptavidin linked allophycocyanin (SA-APC) (From Wallac/PE Life Sciences CAT# AD0059A)
5. 1x FRET Buffer: (20mM $\text{KH}_2\text{PO}_4/\text{K}_2\text{HPO}_4$ pH 7.3, 150mM NaCl, 2.5mM CHAPS, 2mM EDTA, 1mM DTT (add fresh))
6. 96 well or 384 well black multiwell plates (from LJL)

Stock Solutions:

- 10 0.5M $\text{KH}_2\text{PO}_4/\text{K}_2\text{HPO}_4$: pH 7.3
5M NaCl
80mM (5%) CHAPS
0.5M EDTA pH 8.0
1M DTT (keep at -20°C)

15 B. Preparation of Screening Reagents:

- Prepare reaction mixture for the appropriate number of wells by combining the following reagents 5nM / well GST-hLXR α LBD, 5nM / well GST-hLXR β LBD, 5nM / well Anti-GST antibody (Eu), 12nM / well biotin-SRC-1 peptide, 12nM / well APC-SA adjust the volume to 10 μ L/well with 1x-FRET buffer.
- 20

C. Procedure:

- Add 0.5 μ l of a 1mM stock compound (for approx. 10 μ M final concentration) or solvent to each well in a 96 well or 384 well black plate (LJL).
- 25

1. Add 10 μ l reaction mixture (prepared above) to each well of the multiwell plate.

-339-

2. Incubate covered or in the dark (the APC is light sensitive) at room temperature for 1-4hr. After this time if reactions are not read they can be stored at 4 degrees for several more hours without too much loss of signal.

5

3. Read the plate using an LJL Analyst, or similar instrument, using the following conditions:

Channel 1: Excitation is 330nm and emission is 615. This is for Eu
10 chelate

Channel 2: Excitation is 330nm and emission is 665. This is for APC

For channel 1: Flashes per well = 100; Integration time = 1000 μ s;
interval between flashes = 1x10ms; Delay after flash = 200 μ s

15

For channel 2: Flashes per well = 100; Integration time = 100 μ s;
interval between flashes = 1x10ms; Delay after flashes = 65 μ s

Example 72

20 Scintillation proximity assay (SPA):

The SPA assay measures the radioactive signal generated by the binding of ^3H -24, 25-epoxycholesterol to LXR α or LXR β . The basis of the assay is the use of SPA beads containing a scintillant, such that when binding to the receptor brings the labeled ligand into proximity with the bead, the
25 energy from the label stimulates the scintillant to emit light. The light is measured using a standard microplate scintillation reader. The ability of a ligand to bind to a receptor can be measured by assessing the degree to which the compound can compete off a radiolabelled ligand with known affinity for the receptor.

30 A. Required Materials:

1. Label: ^3H -24, 25-epoxy-cholesterol (Amersham)

-340-

2. LXR α lysate: Baculovirus expressed LXR α /RXR heterodimer with RXR having a 6-HIS tag produced as a crude lysate
3. LXR β lysate: Baculovirus expressed LXR β /RXR heterodimer with RXR having a 6-HIS tag produced as a crude lysate
- 5 4. SPA beads: Ysi copper His-tag SPA beads (Amersham)
5. Plates: Non-binding surface 96-well plate (Corning)
6. Protein lysate dilution buffer: (20mM Tris-HCl pH 7.9, 500mM NaCl, 5mM Imidazole).
- 10 7. 2x SPA Buffer: (40mM K₂HPO₄/KH₂PO₄ pH7.3, 100mM NaCl, 0.05% Tween 20, 20% Glycerol, 4mM EDTA)
8. 2x SPA Buffer w/o EDTA: (40mM K₂HPO₄/KH₂PO₄ pH7.3, 100mM NaCl, 0.05% Tween 20, 20% Glycerol)

A. Stock Solutions

- 15 0.5M K₂HPO₄/KH₂PO₄ pH 7.3
0.5M EDTA pH 8.0
5M NaCl
10% Tween-20
Glycerol

20 B. Preparation of Screening Reagents:

- 25 1. [³H] 24,25 Epoxycholesterol (EC) solution. For a single 384-well plate (or 400 wells), add 21 μ l [³H] EC (specific activity 76.5Ci/mmol, concentration 3.2mCi/ml) in 4.4ml of 2x SPA buffer to a final concentration of 200nM. For each additional 384-well plate, add 19.1 μ l additional [³H] EC and 4.0ml additional 2x SPA buffer. The final concentration of [³H] EC in the well will be 50nM.
2. Dilute LXR α lysate with protein lysate dilution buffer. Make 1400 μ l of diluted LXR α lysate for a 384-well plate, (or 200 wells) and 1120 μ l of diluted LXR α lysate for each additional 384-well plate.

-341-

3. Diluted LXR β lysate with protein lysate dilution buffer. Make 1400 μ l of diluted LXR β lysate for 1 a 384-well plate, (or 200 wells) and 1120 μ l of diluted LXR β lysate for each additional 384-well plate.
4. SPA bead solution. For 1 a 384-well plate (or 400 wells), mix 3.75ml of 2x SPA buffer w/o EDTA, 2.25ml of H₂O, and 1.5ml of Ysi His-tag SPA beads (Vortex well before taking). For each addition 384-well plate, mix additional 3.5ml of 2x SPA buffer w/o EDTA, 2.1ml of H₂O, and 1.4ml of Ysi His-tag SPA beads to the SPA bead solution.

C. Procedure:

1. Prepare appropriate dilutions of each compound and pipette into the appropriate wells of a multiwell plate.
2. Add 9.1 μ l of [3H] EC to each well of column 2-23 of the multiwell plate.
3. Add 5 μ l of diluted LXR α lysate to each well of column 2-23 on odd rows of the multiwell plate.
4. Add 5 μ l of diluted LXR β lysate to each well of column 2-23 on even rows of the multiwell plate.
5. Add 17.5 μ l of SPA bead solution to each well of column 2-23 of the multiwell plate.
6. Cover the plates with clear sealer. Place the plates in the MicroBeta.
7. Incubate at room temperature for 1hr.
8. Count using program n ABASE 3H_384DPM. The setting for n ABASE 3H_384DPM is:
Counting Mode: DPM
Sample Type: SPA
ParaLux Mode: low background
Count time: 30sec.

Assays for LXR α and LXR β were performed in the identical manner. The determined K_i represents the average of at least two independent dose response experiments. The binding affinity for each compound may be determined by non-linear regression analysis using the one site competition formula to determine the IC₅₀ where:

-342-

$$Y = \text{Bottom} + \frac{(\text{Top} - \text{Bottom})}{1 + 10^{X - \text{LogIC}_{50}}}$$

- 5 The K_i is then calculated using the Cheng and Prusoff equation where:

$$K_i = \frac{\text{IC}_{50}}{1 + [\text{Ligand}]/K_d}$$

- 10 Ligand = 50nM EC and K_d = 200nM as determined by saturation binding

Example 73

Co-Transfection Assay

- To measure the ability of compounds to activate or inhibit the transcriptional activity of LXR, in a cell based assay, the cotransfection assay
- 15 may be used. It has been shown that LXR functions as a heterodimer with RXR. For the co-transfection assay, expression plasmids for LXR and RXR are introduced via transient transfection into mammalian cells along with a luciferase reporter plasmid that contains one copy of a DNA sequence that is bound by LXR-RXR heterodimers (LXRE; Willy, P. et al. 1995). Treatment of
- 20 transfected cells with an LXR agonist increases the transcriptional activity of LXR, which is measured by an increase in luciferase activity. Similarly, LXR antagonist activity can be measured by determining the ability of a compound to competitively inhibit the activity of a LXR agonist.

A. Required Materials

- 25 1. CV-1 African Green Monkey Kidney Cells
2. Co-transfection Expression plasmids, CMX-hLXR, or CMX-hLXR, CMX-RXR, reporter (LXREx1-Tk-Luciferase), and control (CMX-Galactosidase expression vector).
- 30 3. Transfection reagent such as FuGENE6 (Roche).

-343-

4. 1x Cell lysis buffer (1 % Triton X 100 (JT Baker X200-07), 10% Glycerol (JT Baker M778-07), 5mM Dithiotreitol (Quantum Bioprobe DTT03; add fresh before lysing), 1mM EGTA (Ethylene Glycol-bis (B-Amino ethyl ether)-N,N,N',N'-Tetracetic Acid) (Sigma E-4378), 25mM Tricine (ICN 807420) pH 7.8
5. 1x Luciferase assay buffer (pH at 7.8) (0.73mM ATP , 22.3mM Tricine, 0.11mM EDTA 33.3mM DTT)
6. 1x Luciferrin/CoA (11 mM Luciferin, 3.05mM Coenzyme A, 10 mM HEPES

B. Preparation of Screening Reagents

- 10 1. CV-1 cells are prepared 24 hours prior to the experiment by plating them into T-175 flasks or 500cm² dishes in order to achieve 70-80% confluency on the day of the transfection. The number of cells to be transfected is determined by the number of plates to be screened. Each 384 well plate requires 1.92×10^6 cells or 5000 cells per well.
- 15 2. DNA Transfection Reagent is prepared by mixing the required plasmid DNAs with a cationic lipid transfection reagent such as DOTAP or FuGENE6 by following the instructions provided with the reagents. Optimal DNA amounts need to be determined empirically per cell line and size of vessel to be transfected.
- 20 3. Add 10-12mls media to the DNA Transfection Reagent and add this mixture to the cells after aspirating media from a T175 cm² flask.
4. Incubate at least 5 hours at 37 degrees to prepare screening cells.
5. Luciferase assay reagent is prepared by combining before use (per 10 ml):
- 25 10 ml 1x Luciferase assay buffer
0.54 mls of 1x Luciferrin/CoA
0.54 mls of 0.2 M Magnesium sulfate

-344-

1. C. Procedure

1. Prepare assay plates by dispensing 0.5 μ l of 1mM compound per well of a 384 well plate to achieve final compound concentration of 10 μ M and 1% DMSO.
- 5 2. Remove media from the screening cells, trypsinize, harvest cells by centrifugation, count the cells, and plate at 5000 cells per well in the 384 well assay plate prepared above in a volume of about 45 μ l.
3. Incubate assay plates containing both compounds and screening cells for 20 hours at 37 C degrees.
- 10 4. Carefully aspirate media from cells and ensure that cells are not lifted off.
5. Add lysis buffer (30 μ l/well) and incubate at least 30 minutes room temp.
6. Add luciferase assay buffer (30 μ l/well) and read assay plates on
- 15 luminometer (PE Biosystems Northstar reader with on-board injectors, or equivalent).
7. Read plates immediately after addition of luciferase assay reagent.

The LXR/LXRE co-transfection assay can be used to establish the EC₅₀/IC₅₀ values for potency and percent activity or inhibition for efficacy.

- 20 Efficacy defines the activity of a compound relative to a high control ((N-(3-((4-fluorophenyl)-(naphthalene-2-sulfonyl)-amino)propyl)-2,2-dimethylpropionamide)) or a low control (DMSO/vehicle). The dose response curves are generated from an 8 point curve with concentrations differing by 1/2 LOG units. Each point represents the average of 4 wells of data from a 384
- 25 well plate. The curve for the data is generated by using the equation:

$$Y = \text{Bottom} + (\text{Top} - \text{Bottom}) / (1 + 10^{((\text{LogEC}_{50} - X) * \text{HillSlope}))}$$

- The EC₅₀/IC₅₀ is therefore defined as the concentration at which an agonist or antagonist elicits a response that is half way between the Top (maximum) and Bottom (baseline) values. The EC₅₀/IC₅₀ values represented
- 30 are the averages of at least 3 independent experiments. The determination of the relative efficacy or %control for an agonist is by comparison to the

-345-

maximum response achieved by ((N-(3-((4-fluoro-phen-yl)-(naphthalene-2-sulfonyl)-amino)propyl)-2,2-dimethylpropionamide) that is measured individually in each dose response experiment.

For the antagonist assay, a LXR agonist can be added to each well of a 384 well plate to elicit a response. The %inhibition for each antagonist is therefore a measurement of the inhibition of the activity of the agonist. In this example 100% inhibition would indicate that the activity of a specific concentration of LXR agonist has been reduced to baseline levels, defined as the activity of the assay in the presence of DMSO only.

10

Example 74

In Vivo studies:

In order to evaluate direct regulation of key target genes by the compounds of the invention, animals are administered a single oral dose of the test compound and tissues collected at six or fifteen hours after dose. Male C57BL/6 mice (n=8) are dosed by oral gavage with vehicle or compound. At six and fifteen hours after the dose, animals are bled via the retro orbital sinus for plasma collection. Animals are then euthanized and tissues, such as liver and intestinal mucosa are collected and snap frozen for further analysis. Plasma is analyzed for lipid parameters, such as total cholesterol, HDL cholesterol and triglyceride levels. RNA is extracted for frozen tissues and can be analyzed by quantitative real time PCR for regulation of key target genes. To identify specificity of target gene regulation by LXR subtypes, LXR deficient mice ($LXR\alpha^{-/-}$ or $LXR\beta^{-/-}$) and C57BL/6 wild-type controls are used in this same protocol.

25

Plasma Lipid Evaluation:

To compare the effects of compounds on plasma cholesterol and triglycerides, animals are dosed with compound for one week and plasma lipid levels are monitored throughout the study. Male C57BL/6 mice (n=8) are dosed daily by oral gavage with vehicle or compound. Plasma samples are taken on day -1 (in order to group animals), day 1, 3, and 7. Samples are

30

-346-

- collected three hours after the daily dose. On day 7 of the study, following plasma collection, animals are euthanized and tissues, such as liver and intestinal mucosa are collected and snap frozen for further analysis. Plasma is analyzed for lipid parameters, such as total cholesterol, HDL cholesterol
- 5 and triglyceride levels. RNA is extracted for frozen tissues and can be analyzed by quantitative real time PCR for regulation of key target genes. To identify specificity of target gene regulation by LXR subtypes, LXR deficient mice ($\text{LXR}\alpha^{-/-}$ or $\text{LXR}\beta^{-/-}$) and C57BL/6 wild-type controls are used in this same protocol.
- 10 **Cholesterol Absorption:**
- Evaluation of compounds to inhibit cholesterol absorption is done via measurement of labeled cholesterol in feces. Male A129 mice (n=7) are dosed daily by oral gavage with vehicle or compound for 7 days. On day 7 of
- 15 the study, animals are administered [^{14}C]-cholesterol and [^3H]-sitostanol by oral gavage. Animals are individually housed on wire racks for the next 24 hours in order to collect feces. Feces are then dried and ground to a fine powder. Labeled cholesterol and sitostanol are extracted from the feces and ratios of the two are counted on a liquid scintillation counter in order to
- 20 evaluate the amount of cholesterol absorbed by the individual animal.

-347-

Results of Examples 71, 72 and 73

Most of the compounds disclosed herein and tested exhibited activity in at least one of the above assays (EC_{50} or IC_{50} less than 10 μM). Most showed activity at below 1 μM . Some showed activity below 100 nM. Representative data is shown in the Tables below. K_i 's are determined in a scintillation proximity binding assay (Example 70). EC_{50} and % efficacy are determined in a co-transfection assay (Example 71).

	Compound	$K_i(\alpha)$ μM	$K_i(\beta)$ μM	LXR α /LXRE EC_{50} (μM)
10	1-Cyclohexylideneamino-2-oxo-6-phenyl-4-trifluoromethyl-1,2-dihydropyridine-3-carbonitrile	0.69	0.45	3.4
	1-benzyl-3-cyano-6-(3-methoxyphenyl)-4-trifluoromethyl-1H-pyridin-2-one	0.51	0.12	1.2
15	1-Benzyl-2-oxo-6-thiophen-2-yl-4-trifluoromethyl-1,2-dihydropyridine-3-carbonitrile	1.4	0.58	1.6
20	1-(5-Methyl-furan-2-ylmethyl)-2-oxo-6-phenyl-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile	0.36	0.23	0.58

	Compound	LXR α /LXRE Eff (%)	LXR β /LXRE EC_{50} (μM)	LXR β /LXRE Eff (%)
25	1-Cyclohexylideneamino-2-oxo-6-phenyl-4-trifluoromethyl-1,2-dihydropyridine-3-carbonitrile	90	4.3	72
30	1-benzyl-3-cyano-6-(3-methoxyphenyl)-4-trifluoromethyl-1H-pyridin-2-one	78	0.84	79

-348-

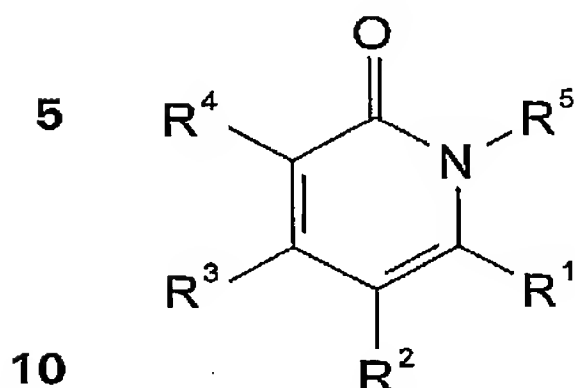
	Compound	LXR α /LXRE Eff (%)	LXR β /LXRE EC ₅₀ (μ M)	LXR β /LXRE Eff (%)
5	1-Benzyl-2-oxo-6-thiophen-2-yl-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile	56	1.8	82
	1-(5-Methyl-furan-2-ylmethyl)-2-oxo-6-phenyl-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile	91	0.81	93

- 10 Since modifications will be apparent to those of skill in this art, it is intended that this invention be limited only by the scope of the appended claims.

-349-

WHAT IS CLAIMED IS:

1. A compound having formula I:



or a pharmaceutically acceptable derivative thereof, wherein

R^1 is selected from substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted aralkyl, substituted or unsubstituted heteroaralkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted cycloalkenyl, substituted or unsubstituted cycloalkynyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted cycloalkylalkyl and substituted or unsubstituted heterocyclylalkyl;

R^2 is hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl;

R^3 and R^4 are selected from (i) or (ii) as follows:

(i) R^3 is substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted alkylaminocarbonyl or $C(J)OR^{30}$; and R^4 is hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, halide, pseudohalide, hydroxycarbonyl, $C(J)R^{30}$, $C(J)NR^{31}R^{32}$, $CH_2NR^{31}R^{32}$, CH_2OR^{31} , $CR^{30}=CR^{31}R^{32}$, NO_2 or $NR^{31}R^{32}$; and

-350-

(ii) R^3 and R^4 , together with the atoms to which they are attached, form a substituted or unsubstituted heterocyclic ring, with the proviso that the heterocyclic ring does not have more than one oxo substituent;

R^5 is substituted or unsubstituted alkyl, substituted or
5 unsubstituted heterocyclyl, substituted or unsubstituted aryl, substituted or unsubstituted aralkyl, substituted or unsubstituted heteroaralkyl, $-N=CR^6R^7$ or $-NR^9R^{10}$;

R^6 and R^7 are each independently hydrogen, substituted or
unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or
10 unsubstituted alkynyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted aralkyl, or substituted or unsubstituted heteroaralkyl; or together form substituted or unsubstituted alkylene, substituted or unsubstituted
15 alkenylene, substituted or unsubstituted alkynylene, or $-(CH_2)_xX(CH_2)_y-$ where x and y are each independently 1, 2 or 3, and X is O, S or NR^8 ;

R^8 is substituted or unsubstituted alkyl, substituted or
unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or
unsubstituted alkylcarbonyl, substituted or unsubstituted arylcarbonyl, or
20 substituted or unsubstituted heteroarylcarbonyl;

R^9 and R^{10} are each independently hydrogen, substituted or
unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or
unsubstituted alkynyl, substituted or unsubstituted aryl, substituted or
unsubstituted heteroaryl, substituted or unsubstituted aralkyl, or
25 substituted or unsubstituted heteroaralkyl; or together form substituted or unsubstituted alkylene, substituted or unsubstituted alkenylene, substituted or unsubstituted alkynylene, or $-(CH_2)_xX(CH_2)_y-$ where x and y are each independently 1, 2 or 3, and X is O, S or NR^8 ;

-351-

R^{30} is hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted cycloalkylalkyl, substituted or unsubstituted heterocyclalkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted aralkyl, or substituted or unsubstituted heteroaralkyl;

R^{31} and R^{32} are each independently hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted cycloalkylalkyl, substituted or unsubstituted heterocyclalkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted aralkyl, substituted or unsubstituted heteroaralkyl, or $C(J)R^{35}$; or R^{31} and R^{32} , together with the atoms to which they are attached, form substituted or unsubstituted cycloalkyl ring, a substituted or unsubstituted heterocyclic ring or a substituted or unsubstituted heteroaryl ring;

J is O, S or NR^{40} ;

R^{35} is hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted alkoxy, substituted or unsubstituted aralkoxy, substituted or unsubstituted alkylamino, substituted or unsubstituted dialkylamino, substituted or unsubstituted arylalkylamino, or substituted or unsubstituted diarylamino;

R^{40} is hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl;

-352-

where the alkyl, alkenyl, alkynyl, cycloalkyl, heterocyclyl, alkylene, alkenylene, alkynylene, aryl, heteroaryl, aralkyl, aralkenyl, aralkynyl, heteroaralkyl, heteroaralkenyl and heteroaralkynyl moieties of R¹, R², R³, R⁵, R⁶, R⁷, R⁸, R⁹ and R¹⁰ are unsubstituted or substituted with one or

5 more substituents, in one embodiment one to three or four substituents, each independently selected from Q¹, where Q¹ is halo, pseudohalo, hydroxy, oxo, thia, nitrile, nitro, formyl, mercapto, amino, hydroxyalkyl, hydroxyalkylaryloxy, hydroxyaryl, hydroxyalkylaryl, hydroxycarbonyl, hydroxycarbonylalkyl, alkyl, haloalkyl, polyhaloalkyl, aminoalkyl,

10 diaminoalkyl, alkenyl containing 1 to 2 double bonds, alkynyl containing 1 to 2 triple bonds, cycloalkyl, cycloalkylalkyl, heterocyclyl, heterocyclylalkyl, aryl, diaryl, hydroxyaryl, alkylaryl, heteroaryl, aralkyl, aralkenyl, aralkynyl, alkylaralkyl, heteroarylalkyl, trialkylsilyl, dialkylarylsilyl, alkyl diarylsilyl, triarylsilyl, alkylidene, arylalkylidene,

15 alkylcarbonyl, alkylarylcarbonyl, arylcarbonyl, heterocyclylcarbonyl, heteroarylcarbonyl, alkoxycarbonyl, alkoxycarbonylalkyl, alkoxycarbonylaryloxy, aryloxycarbonyl, aryloxycarbonylalkyl, heterocyclylcarbonylalkylaryl, aralkoxycarbonyl, aralkoxycarbonylalkyl, arylcarbonylalkyl, aminocarbonyl, alkylaminocarbonyl,

20 dialkylaminocarbonyl, arylaminocarbonyl, diarylaminocarbonyl, arylalkylaminocarbonyl, alkoxy, aryloxy, haloalkoxy, alkoxyaryloxy, alkylaryloxy, diaryloxy, alkylaryloxyalkyl, alkyl diaryloxy, perfluoroalkoxy, alkenyloxy, alkynyloxy, aryloxyalkoxy, aralkoxyaryloxy, alkylarylcycloalkyloxy, heterocycloxy, alkoxyalkyl, alkoxyalkoxyalkyl,

25 alkylheteroaryloxy, alkylcycloalkoxy, cycloalkyloxy, heterocycliloxy, aralkoxy, haloaryloxy, heteroaryloxy, alkylheteroaryloxy, alkoxycarbonylheterocycloxy, alkylcarbonylaryloxy, alkylcarbonyloxy, arylcarbonyloxy, aralkylcarbonyloxy, alkoxycarbonyloxy, aryloxycarbonyloxy, alkoxyaryloxy, aralkoxycarbonyloxy, ureido, alkylureido, aryl-

-353-

ureido, amino, aminoalkyl, alkylaminoalkyl, dialkylaminoalkyl, aryl-
 aminoalkyl, diarylaminoalkyl, alkylarylaminoalkyl, alkylamino, dialkyl-
 amino, haloalkylamino, haloalkylarylamino, arylamino, diarylamino, alkyl-
 arylamino, aralkylamino, alkylcarbonylamino, aralkylcarbonylamino,
 5 haloalkylcarbonylamino, alkoxycarbonylamino, aralkoxycarbonylamino,
 arylcarbonylamino, arylcarbonylaminoalkyl, aryloxycarbonylaminoalkyl,
 aryloxyarylcarbonylamino, aryloxycarbonylamino, alkylenedioxyalkyl,
 dialkylalkylenedioxyalkyl, alkylsulfonylamino, arylsulfonylamino, azido,
 dialkylphosphonyl, alkylarylphosphonyl, diarylphosphonyl, alkylthio, aryl-
 10 thio, perfluoroalkylthio, hydroxycarbonylalkylthio, thiocyano,
 isothiocyano, alkylsulfinyl, alkylsulfonyl, arylsulfinyl, arylsulfonyl,
 aminosulfonyl, alkylaminosulfonyl, dialkylaminosulfonyl,
 arylaminosulfonyl, diarylaminosulfonyl or alkylarylaminosulfonyl; or two
 Q¹ groups, which substitute atoms in a 1,2 or 1,3 arrangement, together
 15 form alkylenedioxy (*i.e.*, -O-(CH₂)_z-O-), thioalkylenoxy (*i.e.*,
 -S-(CH₂)_z-O-) or alkylenedithioxy (*i.e.*, -S-(CH₂)_z-S-) where z is 1 or 2; and
 each Q¹ is independently unsubstituted or substituted with one or
 more substituents, in one embodiment one to three or four substituents,
 each independently selected from Q², where Q² is halo, pseudohalo,
 20 hydroxy, oxo, thia, nitrile, nitro, formyl, mercapto, amino, hydroxyalkyl,
 hydroxyaryl, hydroxycarbonyl, alkyl, haloalkyl, polyhaloalkyl, aminoalkyl,
 diaminoalkyl, alkenyl containing 1 to 2 double bonds, alkynyl containing
 1 to 2 triple bonds, cycloalkyl, heterocyclyl, aryl, heteroaryl, aralkyl,
 aralkenyl, aralkynyl, alkoxycarbonyl, aryloxycarbonyl, aralkoxycarbonyl,
 25 arylcarbonylalkyl, aminocarbonyl, alkoxy, aryloxy, aralkoxy,
 alkylenedioxy, amino, aminoalkyl, dialkylamino, arylamino, diarylamino,
 alkylamino, dialkylamino, haloalkylamino, arylamino, diarylamino, alkyl-
 arylamino, aralkylamino, alkoxycarbonylamino, arylcarbonylamino,
 alkylthio or arylthio.

-354-

2. The compound of claim 1, wherein R¹ is substituted or unsubstituted aryl.

3. The compound of any of claims 1-2, wherein R¹ is substituted or unsubstituted heteroaryl.

5 4. The compound of any of claims 1-3, wherein R¹ is substituted or unsubstituted heterocyclyl.

5. The compound of any of claims 1-4, wherein R¹ is substituted or unsubstituted methyl, substituted or unsubstituted cyclohexyl, substituted or unsubstituted cyclopentenyl, substituted or
10 unsubstituted phenyl, substituted or unsubstituted benzyl, substituted or unsubstituted naphthyl, substituted or unsubstituted furyl, substituted or unsubstituted thienyl, substituted or unsubstituted pyrrolyl, substituted or unsubstituted pyrazolyl, substituted or unsubstituted thiazolyl, substituted or unsubstituted piperidinyl, substituted or unsubstituted
15 pyridinyl, substituted or unsubstituted pyrazinyl, substituted or unsubstituted indanyl, substituted or unsubstituted benzofuryl, substituted or unsubstituted benzothiophenyl or substituted or unsubstituted indolyl, where the substituents are each independently selected from one or more Q¹.

20 6. The compound of any of claims 1-5, wherein R¹ is substituted or unsubstituted phenyl.

7. The compound of any of claims 1-6, wherein R¹ is substituted or unsubstituted furyl, substituted or unsubstituted thienyl, substituted or unsubstituted pyrrolyl, substituted or unsubstituted
25 pyrazolyl, substituted or unsubstituted thiazolyl, substituted or unsubstituted piperidinyl, substituted or unsubstituted pyridinyl, substituted or unsubstituted pyrazinyl, substituted or unsubstituted benzofuryl, substituted or unsubstituted benzothiophenyl or substituted

-355-

or unsubstituted indolyl, where the substituents are each independently selected from one or more Q¹.

8. The compound of any of claims 1-7, wherein R¹ is substituted or unsubstituted thienyl.

5 9. The compound of claim 8, wherein R¹ is thienyl.

10 10. The compound of any of claims 1-9, wherein R¹ is substituted with, in one embodiment one to five, in another embodiment one to three, in another embodiment one or two Q¹, where Q¹ is halo, pseudohalo, nitro, hydroxy, amino, hydroxyalkyl, hydroxyalkylaryloxy, hydroxyaryl, hydroxyalkylaryl, hydroxycarbonyl, haloalkyl, alkyl, heterocyclyl, heterocyclylalkyl, aryl, heteroaryl, aralkyl, heteroaralkyl, alkylaralkyl, alkylarylcarbonyl, heterocyclylcarbonyl, alkoxycarbonyl, alkoxycarbonylaryloxy, aryloxy, heterocyclylcarbonylalkylaryl, aralkoxycarbonyl, alkoxy, aryloxy, heteroaryloxy, aralkoxy, alkylaryloxy, alkylaryloxyalkyl, alkylidaryloxy, aryloxyalkoxy, aralkoxyaryloxy, alkylarylcyloalkoxy, alkylheteroaryloxy, cycloalkoxy, heterocyclylalkoxy, heterocycliloxy, haloaryloxy, alkylcarbonylaryloxy, arylamino, alkylarylamine, aralkylamine, alkylcarbonylamine, alkylaminocarbonyl, haloalkylcarbonylamine, or arylthio; and each Q¹ is
 15 unsubstituted or further substituted with Q², which is hydrogen, alkyl, aryl, alkoxy, hydroxycarbonyl, alkoxycarbonyl, pseudohalide, halo, aryloxy, aralkoxy, haloalkyl, alkylthio, alkylamine, dialkylamine or
 20 hydroxy.

25 11. The compound of any of claims 1-10, wherein R¹ is substituted with Q¹, which is selected from alkoxycarbonylaryloxy, aryl-oxy, alkylaryloxy, alkylaryloxyalkyl, alkylidaryloxy, aryloxyalkoxy, aralkoxyaryloxy, alkylarylcyloalkoxy, alkylheteroaryloxy, cycloalkoxy, heterocyclylalkoxy, heterocycliloxy, heteroaryloxy, haloaryloxy, alkoxycarbonylheterocycliloxy, alkylcarbonylaryloxy, dialkylaminoaryloxy,

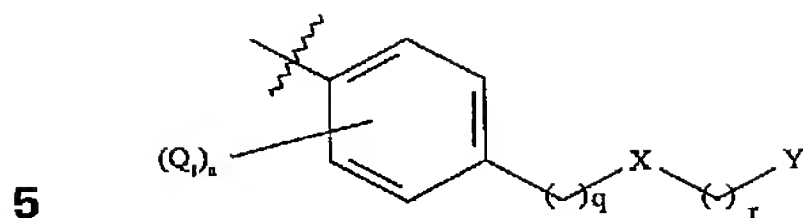
-356-

alkoxyaryloxy, cyanoaryloxy, aryloxyaryloxy, dialkylaryloxy, haloalkylaryloxy, alkylthioaryloxy, alkylaryl amino, hydroxyaryloxy, aryl amino, alkyl amino, aralkyl amino and arylthio.

12. The compound of any of claims 1-11, wherein R¹ is
- 5 substituted with Q¹, which is selected from methyl, ethyl, trifluoromethyl, nitro, hydroxy, n-butyloxy, 3-(2-piperidinyl)ethoxy, methylcarbonylamino, ethylaminocarbonylamino, chloro, bromo, benzylamino, methylphenoxymethyl, trifluoromethylcarbonylamino, methoxycarbonyl, phenoxy, cyano, n-butoxy, benzoxy, 1-piperidinyl,
- 10 methoxy, hydroxycarbonyl, tert-butoxycarbonylpiperazinylcarbonyl, hydroxymethyl, 1-piperidinylcarbonyl, phenyl, methylphenyl, dimethylamino, methylcarbonylamino, methoxyphenoxy, methylphenoxy, piperidinylmethyl, biphenoxy, benzoxy carbonyl, piperazinylcarbonyl, benzyl, phenylthio, chlorophenoxy, methylbenzyl,
- 15 hydroxymethylphenoxy, ethoxycarbonylphenoxy, tertbutylmethylphenoxy, tertbutylbiphenoxy, ethylphenoxy, isopropylphenoxy, tertbutylphenoxy, N,N-dimethylphenoxy, N,N-phenylmethylamino, 3-methylphenyl-1-amino, trifluoromethylphenoxy, ethylphenoxy, methylcarbonylphenoxy, tetrahydropyranyloxy,
- 20 tetrahydronaphthoxy, hydroxycarbonylphenoxy, 1,3-hexafluoro-2-hydroxypropylphenylamino, benzoxyphenoxy, cyclohexyloxy, indanyloxy, methoxycarbonylphenoxy, isopropylphenoxy, tert-butylphenoxy, N,N-dimethylaminophenoxy, methoxyphenoxy, methoxycarbonylphenoxy, cyanophenoxy, fluorophenoxy, benzoxyphenoxy, trifluoromethylphenoxy,
- 25 bromophenoxy, 3,5-ditrifluoromethylphenoxy, methylthiophenoxy, indolyl, tert-butoxycarbonyl-piperidinyl, hydroxyphenoxy, pyrimidinoxy and pyrazinoxy.

13. The compound of any of claims 1-12, wherein R¹ has formula II:

-357-



where, q and r are each independently an integer from 0 to 5, or from 0 to 3, or 0 or 1; n is an integer from 0 to 4, in one embodiment 0 to 2, in
 10 another embodiment 0 or 1; X is O, S or NR' , where R' is alkyl, aryl or hydrogen; Y is substituted or unsubstituted alkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted heterocyclyl or substituted or unsubstituted cycloalkyl, where the substituents, when present are each independently selected
 15 from one or more Q^1 .

14. The compound of claim 13, wherein q and r are each independently an integer from 0 to 3.

15. The compound of any of claims 13-14, wherein q and r are each independently 0 or 1.

20 16. The compound of any of claims 13-15, wherein n is 1 to 3.

17. The compound of any of claims 13-16, wherein n is 1.

18. The compound of any of claims 13-17, wherein X is O.

19. The compound of any of claims 13-18, wherein X is S.

20. The compound of any of claims 13-19, wherein X is NR' .

25 21. The compound of claim 20, wherein R' is alkyl or hydrogen.

22. The compound of any of claims 20-21, wherein R' is lower alkyl or hydrogen.

23. The compound of any of claims 20-22, wherein R' is hydrogen.

-358-

24. The compound of claim 13, wherein Y is substituted or unsubstituted heteroaryl, where the substituents, when present are each independently selected from one or more Q¹.

25. The compound of any of claims 13 and 24, wherein Y is
5 substituted or unsubstituted heterocyclyl, where the substituents, when present are each independently selected from one or more Q¹.

26. The compound of any of claims 13 and 24-25, wherein Y is substituted or unsubstituted aryl, where the substituents, when present are each independently selected from one or more Q¹.

10 27. The compound of any of claims 13 and 24-26, wherein Y is substituted or unsubstituted phenyl, where the substituents, when present are each independently selected from one or more Q¹.

28. The compound of any of claims 13 and 24-27, wherein Y is substituted with Q¹, which is selected from halo, hydroxy, alkyl, alkoxy,
15 alkoxycarbonyl, haloalkyl, alkylcarbonyl, hydroxycarbonyl, hydroxyhaloalkyl, aryl, aralkoxy, alkylaryl, alkylheteroaryl and heteroaryl.

29. The compound of any of claims 1-28, wherein R¹ is substituted or unsubstituted phenyl, substituted or unsubstituted naphthyl, substituted or unsubstituted furyl, substituted or unsubstituted
20 thienyl, or substituted or unsubstituted pyrrolyl, where the substituents are selected from one or more Q¹.

30. The compound of any of claims 1-29, wherein R¹ is methyl, cyclohexyl, 1-cyclopentenyl, indanyl, phenyl, 1-naphthyl, 2-naphthyl, 3-methylphenyl, 2-chlorophenyl, 4-chlorophenyl, 3-ethylphenyl, 3-
25 trifluoromethylphenyl, 3-nitrophenyl, 3-hydroxyphenyl, 3-n-butoxyphenyl, 3-benzyloxyphenyl, 3-(2-piperidinyloxy)phenyl, 3-methylcarbonylaminophenyl, 3-ethylaminocarbonylaminophenyl, 2-methylphenyl, 2-methoxyphenyl, 4-methylphenyl, 3-methoxyphenyl, 4-methoxyphenyl, 3-chlorophenyl, 4-chlorophenyl, 3-benzylaminophenyl, 3-(3-

-359-

- methyl)phenoxy)methylphenyl, benzyl, 3-trifluoromethylcarbonylaminophenyl, 3,5-dimethylphenyl, 2-chloro-3-methylphenyl, phenylethyl, 4-butoxyphenyl, 4-methoxycarbonylphenyl, 4-phenoxyphenyl, 4-cyanophenyl, 4-benzoxyphe-
5 nyl, 4-(1-piperidinyl)phenyl, 4-hydroxycarbonylphenyl, 4-(4-tert-butoxycarbonylpiperazin-1-ylcarbonyl)phenyl, 4-hydroxymethylphenyl, 4-(1-piperidinylcarbonyl)phenyl, 4-dimethylaminophenyl, 4-methylcarbonylaminophenyl, 4-nitrophenyl, 6-(1,2,3,4-tetrahydro)naphthyl, 4-(4-methoxyphenoxy)phenyl, 4-(2-methylphenoxy)phenyl, 4-(3-methylphenoxy)phenyl, 4-(4-methylphenoxy)phenyl, 4-(3-methoxyphenoxy)phenyl, 4-(1-piperidinylmethyl)phenyl, 4-(4-biphenoxy)phenyl, 3-(1-benzoxycarbonyl)-
10 piperidinyl, 4-(1-piperazinylcarbonyl)phenyl, 5-(2-methyl-2,3-dihydro)benzofuryl, 4-benzylphenyl, 4-phenylthiophenyl, 4-(4-chlorophenoxy)-2-chlorophenyl, 4-(3-biphenoxy)phenyl, 4-(1-benzoxycarbonyl)-piperidinyl, 4-piperidinyl, 4-(1-(3-methylbenzyl))-
15 piperidinyl, 4-(3-methyl-4-hydroxyphen-1-oxy)phenyl, 4-(2-methyl-4-hydroxyphenoxy)phenyl, 4-(4-ethoxycarbonylphenoxy)phenyl, 4-(2-methyl-4-tertbutylphenoxy)phenyl, 4-(2-phenyl-4-
20 tertbutylphenoxy)phenyl, 4-(3-ethylphenoxy)phenyl, 4-(3-isopropylphenoxy)phenyl, 4-(3-tertbutylphenoxy)phenyl, 4-(3,5-dimethylphenoxy)phenyl, 4-phenoxy-2-methylphenyl, 4-(2-methylphenoxy)-2-methylphenyl, 4-(2-methylphenoxy)-3-methylphenyl, 4-N-methyl-N-phenylaminophenyl, 4-(3-trifluoromethylphenoxy)phenyl, 4-
25 (4-ethylphenoxy)phenyl, 4-(4-isopropylphenoxy)phenyl, 4-(4-tertbutylphenoxy)phenyl, 4-(3-methylcarbonylphenoxy)phenyl, 4-(3,4-dimethylphenoxy)phenyl, 4-(2-tetrahydropyranyloxy)phenyl, 4-(2-tetrahydropyranyloxy)-3-methylphenyl, 4-hydroxyphenyl, 3-methyl-4-hydroxyphenyl, 4-(4-methylphenoxy)-3-methylphenyl, 4-(2-

-360-

- ethylphenoxy)phenyl, 4-(2-isopropylphenoxy)phenyl, 4-(5,6,7,8-tetrahydronaphthyloxy)phenyl, 4-(3-hydroxycarbonylphenoxy)phenyl, 2-methyl-4-hydroxyphenyl, 4-phenoxy-2-hydroxyphenyl, 3-phenoxyphenyl, 4-(4-(1,3-hexafluoro-2-hydroxypropyl)phenylamino)phenyl, 4-(2,3,4-trimethylphenoxy)phenyl, 4-(4-benzyloxyphenoxy)phenyl, 4-(3-(methyl-3-indanyloxy)phenyl, 4-(2-methyl-5-benzothiazoloxy)phenyl, 4-cyclohexyloxyphenyl, 4-(3-methoxycarbonylphenoxy)phenyl, 4-(3-isopropylphenoxy)-3-methylphenyl, 4-tert-butyl-phenoxy-3-methylphenyl, 4-N,N-dimethylaminophenoxy-3-methylphenyl, 4-methoxy-phenoxy-3-methylphenyl, 3-methoxy-phenoxy-3-methylphenyl, 4-(3-methoxycarbonyl-phenoxy)-3-methylphenyl, 4-(3-cyanophenoxy)-3-methylphenyl, 4-(4-fluorophenoxy)-3-methylphenyl, 4-(4-benzoxy-phenoxy)-3-methylphenyl, 4-(3-benzoxy-phenoxy)-3-methylphenyl, 4-(2,5-dimethylphenoxy)-3-methylphenyl, 4-(2-chlorophenoxy)-3-methylphenyl, 4-(3-chlorophenoxy)-3-methylphenyl, 4-(2-trifluoromethylphenoxy)-3-methylphenyl, 4-(3-trifluoromethylphenoxy)-2-methylphenyl, 4-(3-bromophenoxy)-phenyl, 4-(4-bromophenoxy)-phenyl, 4-(3-benzyloxy-phenoxy)-phenyl, 4-(3-cyanophenoxy)-phenyl, 4-(4-cyanophenoxy)phenyl, 4-(2,4-dimethylphenoxy)-phenyl, 4-(3,5-trifluoromethylphenoxy)phenyl, 4-(4-methylthio-phenoxy)-phenyl, 4-(4-N,N-dimethylamino-phenoxy)-phenyl, 5-indolyloxyphenyl, 4-(1-tert-butoxycarbonyl-piperidin-4-oxy)-phenyl, 4-(4-hydroxyphenoxy)-phenyl, 4-(2-pyrimidinoxy)-phenyl, 4-(2-pyrazinoxy)-phenyl, 2-thienyl, 2-(5-chloro)thienyl, 2-(5-bromo)thienyl, 2-(5-phenyl)thienyl, 3-benzothiophenyl, 3-methyl-2-benzothiophenyl, 2-(5-(3-methylphenyl))-thienyl, 3-pyridinyl, 2-pyrazinyl, 4-(1-phenyl-5-methyl)pyrazolyl, 2-(1-methyl)pyrrolyl, 3-(1-methyl)indolyl, 3-(1-benzyloxycarbonyl)-piperidinyl, 4-(1-benzyloxyarbonyl)-piperidinyl, 4-piperidinyl, 4-(1-(3-methylbenzyl)-

-361-

piperidiny, 2-furyl, 2-(5-methyl)-furyl, 3-(2,5-dimethyl)-furyl, benzofuryl, 3-(2,4-dimethyl)-furyl, 2-(1,3-thiazolyl) or 5-(2,4-dimethyl)-1,3-thiazolyl.

32. The compound of any of claims 1-31, wherein R¹ is phenyl, 1-naphthyl, 2-naphthyl, 3-methylphenyl, 3-methoxyphenyl, 2-chlorophenyl, 3-ethylphenyl, 3-trifluoromethylphenyl, 3-nitrophenyl, 3-hydroxyphenyl, 3-n-butoxyphenyl, 3-benzyloxyphenyl, 3-(2-piperidinyl)ethoxyphenyl, 3-methylcarbonylaminophenyl, 3-ethylaminocarbonylaminophenyl, 2-methylphenyl, 2-methoxyphenyl, 4-methylphenyl, 3-methoxyphenyl, 4-methoxyphenyl, 3-chlorophenyl or 4-chlorophenyl.

33. The compound of any of claims 1-32, wherein R¹ is 3-(3-methyl)phenoxyethylphenyl, 4-phenoxyphenyl, 4-benzyloxyphenyl, 4-(4-methoxyphenoxy)phenyl, 4-(2-methylphenoxy)phenyl, 4-(3-methylphenoxy)phenyl, 4-(4-methylphenoxy)phenyl, 4-(3-methoxyphenoxy)phenyl, 4-(4-biphenoxy)phenyl, 4-(4-chlorophenoxy)-2-chlorophenyl, 4-(3-biphenoxy)phenyl, 4-(3-methyl-4-hydroxyphenoxy)phenyl, 4-(2-methyl-4-hydroxyphenoxy)phenyl, 4-(4-ethoxycarbonylphenoxy)phenyl, 4-(2-methyl-4-tertbutylphenoxy)phenyl, 4-(2-phenyl-4-tertbutylphenoxy)phenyl, 4-(3-ethylphenoxy)phenyl, 4-(3-isopropylphenoxy)phenyl, 4-(3-tertbutylphenoxy)phenyl, 4-(3,5-dimethylphenoxy)phenyl, 4-phenoxy-2-methylphenyl, 4-(2-methylphenoxy)-2-methylphenyl, 4-(2-methylphenoxy)-3-methylphenyl, 4-(3-trifluoromethylphenoxy)phenyl, 4-(4-ethylphenoxy)phenyl, 4-(4-isopropylphenoxy)phenyl, 4-(4-tertbutylphenoxy)phenyl, 4-(3-methylcarbonylphenoxy)phenyl, 4-(3,4-dimethylphenoxy)phenyl, 4-(4-methylphenoxy)-3-methylphenyl, 4-(2-ethylphenoxy)phenyl, 4-(2-isopropylphenoxy)phenyl, 4-(5,6,7,8-tetrahydronaphthyloxy)phenyl, 4-(3-hydroxycarbonylphenoxy)phenyl, 2-methyl-4-hydroxyphenyl, 4-phenoxy-2-hydroxyphenyl, 3-phenoxyphenyl, 4-(2,3,4-trimethylphenoxy)phenyl, 4-

-362-

- (4-benzyloxyphenoxy)phenyl, 4-(3-methoxycarbonylphenoxy)phenyl, 4-(3-isopropylphenoxy)-3-methylphenyl, 4-tert-butyl-phenoxy-3-methylphenyl, 4-N,N-dimethylaminophenoxy-3-methylphenyl, 4-methoxy-phenoxy-3-methylphenyl, 3-methoxy-phenoxy-3-methylphenyl, 4-(3-methoxycarbonyl-phenoxy)-3-methylphenyl, 4-(3-cyanophenoxy)-3-methylphenyl, 4-(4-fluorophenoxy)-3-methylphenyl, 4-(4-benzyloxy-phenoxy)-3-methylphenyl, 4-(3-benzyloxy-phenoxy)-3-methylphenyl, 4-(2,5-dimethylphenoxy)-3-methylphenyl, 4-(2-chlorophenoxy)-3-methylphenyl, 4-(3-chlorophenoxy)-3-methylphenyl, 4-(2-trifluoromethylphenoxy)-3-methylphenyl, 4-(3-trifluoromethylphenoxy)-2-methylphenyl, 4-(3-bromophenoxy)-phenyl, 4-(4-bromophenoxy)-phenyl, 4-(3-benzyloxy-phenoxy)-phenyl, 4-(3-cyanophenoxy)-phenyl, 4-(4-cyanophenoxy)phenyl, 4-(2,4-dimethylphenoxy)-phenyl, 4-(3,5-trifluoromethylphenoxy)phenyl, 4-(4-methylthio-phenoxy)-phenyl or 4-(4-N,N-dimethylamino-phenoxy)-phenyl.

34. The compound of any of claims 1-33, wherein R¹ is 4-N-methyl-N-phenylaminophenyl, 4-(4-(1,3-hexafluoro-2-hydroxypropyl)phenyl-1-amino)phenyl or 4-phenylthiophenyl.

35. The compound of any of claims 1-34, wherein R¹ is 2-thienyl, 2-(5-chloro)thienyl, 2-(5-bromo)thienyl, 2-(5-phenyl)thienyl, 3-benzothiophenyl, 3-methyl-2-benzothiophenyl or 2-(5-(3-methylphenyl))-thienyl.

36. The compound of any of claims 1-35, wherein R¹ is 2-thienyl.

37. The compound of any of claims 1-36, wherein R¹ is 3-pyridinyl, 2-pyrazinyl, 4-(1-phenyl-5-methyl)pyrazolyl, 2-(1-methyl)pyrrolyl, 3-(1-methyl)indolyl, 3-(1-benzyloxycarbonyl)-piperidinyl, 4-(1-benzyloxycarbonyl)-piperidinyl, 4-piperidinyl or 4-(1-(3-methylbenzyl)-piperidinyl).

-363-

38. The compound of any of claims 1-39, wherein R¹ is 2-furyl, 2-(5-methyl)-furyl, 3-(2,5-dimethyl)-furyl, benzofuryl or 3-(2,4-dimethyl)-furyl.

40. The compound of any of claims 1-39, wherein R¹ is 2-thiazolyl or 5-(2,4-dimethyl)thiazolyl.

41. The compound of any of claims 1-41, wherein R¹ is substituted or unsubstituted phenyl, substituted or unsubstituted naphthyl, substituted or unsubstituted furyl, substituted or unsubstituted thienyl, or substituted or unsubstituted pyrrolyl, where the substituents are selected from one or more Q¹.

42. The compound of any of claims 1-41, wherein R¹ is substituted or unsubstituted phenyl, substituted or unsubstituted naphthyl, or substituted or unsubstituted thienyl, where the substituents are selected from one or more Q¹.

43. The compound of any of claims 1-42, wherein R¹ is substituted with Q¹, which is selected from alkyl, alkoxy, halo, pseudohalo, haloalkyl, nitro, hydroxy, alkoxy, aralkoxy, heterocyclalkoxy, alkylcarbonylamino and alkylaminocarbonylamino.

44. The compound of any of claims 1-43, wherein R¹ is substituted with Q¹, which is selected from methyl, methoxy, chloro, ethyl, trifluoromethyl, nitro, hydroxy, n-butoxy, 3-(2-piperidinyloxy), methylcarbonylamino or ethylaminocarbonylamino.

45. The compound of any of claims 1-44, wherein R² is alkyl or hydrogen.

46. The compound of any of claims 1-45, wherein R² is lower alkyl or hydrogen.

47. The compound of any of claims 1-46, wherein R² is hydrogen.

-364-

48. The compound of any of claims 1-47, wherein R^3 is substituted or unsubstituted alkyl, substituted or unsubstituted alkylaryl, substituted or unsubstituted aryl, substituted or unsubstituted alkoxy carbonyl or substituted or unsubstituted alkylaminocarbonyl, where
5 the substituents are each independently selected from one or more Q^1 .

49. The compound of any of claims 1-48, wherein R^3 is substituted or unsubstituted aryl or substituted or unsubstituted alkoxy carbonyl, where the substituents are each independently selected from one or more Q^1 .

10 50. The compound of any of claims 1-49, wherein R^3 is haloalkyl.

51. The compound of any of claims 1-50, wherein R^3 is substituted with Q^1 , which are selected from halo, pseudohalo, alkyl, alkoxy, alkoxy carbonyl and aryloxy carbonyl.

15 52. The compound of any of claims 1-51, wherein R^3 is substituted with one or more Q^1 , which are selected from halo.

53. The compound of any of claims 1-52, wherein R^3 is substituted with one or more Q^1 , which are selected from fluoro, chloro, phenyl, methyl, methoxy and methylamino.

20 54. The compound of any of claims 1-53, wherein R^3 is perfluoroalkyl.

55. The compound of any of claims 1-54, wherein R^3 is methyl, trifluoromethyl, pentafluoroethyl, heptafluoropropyl, chlorodifluoromethyl, 1-(1-methoxy-1-fluoro)ethyl, methoxy carbonyl, ethoxy carbonyl,
25 methylaminocarbonyl, dimethoxymethyl, methoxy carbonylmethyl or phenyl.

56. The compound of any of claims 1-55, wherein R^3 is trifluoromethyl or pentafluoroethyl.

-365-

57. The compound of any of claims 1-56, wherein R^3 is trifluoromethyl.

58. The compound of any of claims 1-57, wherein R^4 is hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted alkynyl, pseudohalide, $C(J)OR^{30}$, $CH_2NR^{31}R^{32}$ or NO_2 , where the substituents are each independently selected from one or more Q^1 .

59. The compound of any of claims 1-58, wherein R^4 is substituted or unsubstituted methyl, substituted or unsubstituted acetyl or cyano, where the substituents are each independently selected from one or more Q^1 .

60. The compound of any of claims 1-59, wherein R^4 is substituted or unsubstituted methyl, where the substituents are each independently selected from one or more Q^1 .

61. The compound of any of claims 1-60, wherein R^4 is substituted or unsubstituted acetyl, where the substituent is trialkylsilyl.

62. The compound of any of claims 1-61, wherein R^4 is substituted with Q^1 , which is selected from trialkylsilyl, alkylcarbonylamino, arylcarbonylamino, aralkylcarbonylamino, alkoxycarbonylamino, dialkylamino, alkylamino and amino.

63. The compound of any of claims 1-62, wherein R^4 is alkylcarbonylaminoalkyl, alkoxycarbonylaminoalkyl, aralkoxycarbonylaminoalkyl or aryloxycarbonylaminoalkyl.

64. The compound of any of claims 1-63, wherein R^4 is hydrogen, cyano, nitro, hydroxycarbonyl, trimethylsilylacetyl, acetyl, methylcarbonylaminomethyl, ethylcarbonylaminomethyl, n-propylcarbonylaminomethyl, isopropylcarbonylaminomethyl, n-octylcarbonylaminomethyl, phenylcarbonylaminomethyl, benzylcarbonylaminomethyl, phenylethylcarbonylaminomethyl, ethoxycarbonylaminomethyl dimethylaminomethyl or aminomethyl.

-366-

65. The compound of any of claims 1-64, wherein R^4 is cyano.

66. The compound of any of claims 1-65, wherein R^3 and R^4 , together with the atoms to which they are attached, form a substituted or unsubstituted heterocyclic ring, with the proviso that the heterocyclic
5 ring does not have more than one oxo substituent.

67. The compound of any of claims 1-66, wherein R^3 and R^4 , together with the atoms to which they are attached, form a heterocyclic ring substituted with an oxo group.

68. The compound of any of claims 1-67, wherein R^3 and R^4
10 together with the atoms to which they are attached form 2-oxo-tetrahydropyridine or 2-oxo-pyrrol.

69. The compound of any of claims 1-68, wherein R^5 is substituted or unsubstituted alkyl, substituted or unsubstituted aralkyl, substituted or unsubstituted aryl, substituted or unsubstituted
15 heterocyclyl, substituted or unsubstituted heterocyclylalkyl, substituted or unsubstituted heteroaryl, substituted or unsubstituted heteroaralkyl, $-N=CR^6R^7$ or $-NR^9R^{10}$, where the substituents are each independently selected from one or more Q^1 .

70. The compound of any of claims 1-69, wherein R^5 is
20 substituted or unsubstituted aralkyl, where the substituents are each independently selected from one or more Q^1 .

71. The compound of any of claims 1-70, wherein R^5 is substituted or unsubstituted heteroaralkyl, where the substituents are each independently selected from one or more Q^1 .

25 72. The compound of any of claims 1-71, wherein R^5 is substituted or unsubstituted heterocyclylalkyl, where the substituents are each independently selected from one or more Q^1 .

-367-

73. The compound of any of claims 1-72, wherein R^5 is substituted or unsubstituted heterocyclyl, where the substituents are each independently selected from one or more Q^1 .

74. The compound of any of claims 1-73, wherein R^5 is substituted or unsubstituted N-heterocyclyl, where the substituents are each independently selected from one or more Q^1 .

75. The compound of any of claims 1-74, wherein R^5 is $-N=CR^6R^7$.

76. The compound of any of claims 1-75, wherein R^5 is substituted or unsubstituted methyl, substituted or unsubstituted ethyl, substituted or unsubstituted propyl, substituted or unsubstituted phenyl, substituted or unsubstituted piperidinyl, substituted or unsubstituted benzyl, substituted or unsubstituted 2-phenethyl, substituted or unsubstituted 1-phenethyl, substituted or unsubstituted 3-phenylpropyl, substituted or unsubstituted 1,2,3,4-tetrahydro-1-naphthyl, substituted or unsubstituted 3-pyridylmethyl, substituted or unsubstituted 4-pyridylmethyl, substituted or unsubstituted 2-pyrazinyl, substituted or unsubstituted thiazolylmethyl, substituted or unsubstituted oxazolylmethyl, where the substituents are each independently selected from one or more Q^1 .

77. The compound of any of claims 1-76, wherein R^5 is substituted or unsubstituted piperidinyl, substituted or unsubstituted 3-pyridylmethyl, substituted or unsubstituted 4-pyridylmethyl, substituted or unsubstituted 2-pyrazinyl, substituted or unsubstituted thiazolylmethyl, or substituted or unsubstituted oxazolylmethyl, where the substituents are each independently selected from one or more Q^1 .

78. The compound of any of claims 1-77, wherein R^5 is substituted or unsubstituted phenyl, substituted or unsubstituted benzyl,

-368-

substituted or unsubstituted 2-phenethyl, substituted or unsubstituted 1-phenethyl, substituted or unsubstituted 3-phenylpropyl, or $-N=CR^6R^7$.

79. The compound of any of claims 1-78, wherein R^5 is substituted or unsubstituted benzyl, or $-N=CR^6R^7$, where the
5 substituents are each independently selected from one or more Q^1 .

80. The compound of any of claims 1-79, R^5 is substituted with Q^1 , where Q^1 is selected from alkyl, haloalkyl, halohydroxyalkyl, alkoxy, alkoxyalkoxyalkyl, alkoxyalkyl, aryl, halo, alkoxycarbonyl, alkylthio, aryloxy, haloalkoxy, aralkyl, heteroaryl, hydroxy, hydroxyalkyl,
10 heterocyclyl, heterocyclylalkyl, alkylcarbonyl, arylcarbonyl, alkylalkelenedioxy and dialkylalkelenedioxy.

81. The compound of any of claims 1-80, R^5 is substituted with Q^1 , where Q^1 is alkyl, haloalkyl, alkoxy, aryl, halo, alkoxycarbonyl, alkylthio, aryloxy, haloalkoxy, aralkyl, heteroaryl, hydroxy, alkylcarbonyl
15 or arylcarbonyl.

82. The compound of any of claims 1-81, R^5 is substituted with Q^1 , where Q^1 is selected from methyl, isopropyl, trifluoromethyl, methoxy, fluoro, bromo, methoxycarbonyl, chloro, methylthio, phenoxy, trifluoromethoxy, 3-pyridyl, 4-pyridyl, 2-pyridyl, ethyl, n-propyl,
20 cyclohexyl, n-propyloxymethyl, n-pentyloxymethyl, n-octyloxymethyl, ethoxymethyl, n-butoxymethyl, n-hexyloxymethyl, n-octyloxymethyl, tert-butyl, ethoxycarbonyl, methylcarbonyl, hydroxy, phenyl, benzyl, n-butyl, ethoxy, phenylcarbonyl, 2-(2-methyl)-methylenedioxy, 1-piperidinyl, 5-(2,2-dimethyl)-methylenedioxy, methoxymethoxymethyl, hydroxymethyl,
25 hydroxyethyl, methoxymethyl, 1-piperidinylmethyl and 1,3-trifluoro-2-hydroxypropyl.

83. The compound of any of claims 1-82, R^5 is substituted with Q^1 , where Q^1 is selected from methyl, trifluoromethyl, methoxy, fluoro, bromo, methoxycarbonyl, chloro, methylthio, phenoxy, trifluoromethoxy,

-369-

3-pyridyl, 4-pyridyl, 2-pyridyl, ethyl, tert-butyl, ethoxycarbonyl, methylcarbonyl, hydroxy, phenyl, benzyl, n-butyl, ethoxy and phenylcarbonyl.

84. The compound of any of claims 1-83, wherein R⁵ is 2,4-
- 5 dimethylbenzyl, 4-isopropylbenzyl, 4-tert-butylbenzyl, 2,4,5-trifluorobenzyl, 1-naphthylmethyl, 4-(2-(2-methyl)-1,3-dioxymethylene)benzyl, 4-methylbenzyl, 4-ethylbenzyl, 1-piperidinyl, 4-methylcarbonylbenzyl, 5-(2,2-dimethyl)-1,3-dioxymethelenemethyl, 1,2-dihydroxypropanyl, benzyl, 4-(2-methyl)-thiazolylmethyl, 4-(2-
- 10 phenyl)thiazolylmethyl, 3-methoxymethoxymethylbenzyl, 3-hydroxymethylbenzyl, 4-hydroxymethylbenzyl, 4-hydroxyethylbenzyl, 4-methoxymethylbenzyl, 4-(1-piperidinylmethyl)benzyl, 3-biphenyl, 4-biphenyl, 4-(1,3-trifluoro-2-hydroxypropyl)phenyl, 4-(2-ethyl)thiazolylmethyl, 4-(2-isopropyl)thiazolylmethyl, 4-(2-
- 15 propyl)thiazolylmethyl, 4-(2-benzyl)thiazolylmethyl, 4-(2-methyl)oxazolylmethyl, 4-(2-ethyl)oxazolylmethyl, 4-(2-propyl)oxazolylmethyl, 4-(2-phenyl)oxazolylmethyl, 4-(2-benzyl)oxazolylmethyl, 4-(2-cyclohexyl)oxazolylmethyl, 4-n-propyloxymethylbenzyl, 2-(5-methyl)pyrazinylmethyl, 4-n-
- 20 pentyloxymethylbenzyl, 4-n-octyloxymethylbenzyl, 3-ethoxymethylbenzyl, 3-n-butoxymethylbenzyl, 3-n-hexyloxymethylbenzyl, 3-n-octyloxymethylbenzyl, 2-methylbenzyl, 4-methylbenzyl, 3-methylbenzyl, phenylethyl, 4-(2,5-dimethyl)thiazolylmethyl, 4-(2-isopropyl-5-methyl)thiazolylmethyl, 4-(2-ethyl-5-methyl)thiazolylmethyl,
- 25 4-(2-methyl-5-ethyl)thiazolylmethyl, 4-(2,5-diethyl)thiazolylmethyl, phenyl, 2-phenylethyl, 3-phenylpropyl, benzyl, 3-methylbenzyl, 2-trifluoromethylbenzyl, 3-trifluoromethylbenzyl, 4-trifluoromethylbenzyl, 2-methoxybenzyl, 3-methoxybenzyl, 4-methoxybenzyl, 4-phenylbenzyl, 1-phenylethyl, 1,2,3,4-tetrahydro-1-naphthyl, 2-fluorobenzyl, 4-

-370-

fluorobenzyl, 2,4-difluorobenzyl, 4-bromobenzyl, 4-methoxycarbonylbenzyl, 2-chlorobenzyl, 4-chlorobenzyl, 4-methylthiobenzyl, 4-phenoxybenzyl, 4-trifluoromethoxybenzyl, 3-pyridylmethyl or 4-pyridylmethyl.

- 5 85. The compound of any of claims 1-84, wherein R⁵ is 4-(2-(2-methyl)-1,3-dioxymethylene)benzyl, 1-piperidinyl, 5-(2,2-dimethyl)-1,3-dioxymethylenemethyl, 4-(2-methyl)-thiazolylmethyl, 4-(2-phenyl)thiazolylmethyl, 4-(1-piperidinylmethyl)benzyl, 4-(2-ethyl)thiazolylmethyl, 4-(2-isopropyl)thiazolylmethyl, 4-(2-propyl)thiazolylmethyl, 4-(2-benzyl)thiazolylmethyl, 4-(2-methyl)oxazolylmethyl, 4-(2-ethyl)oxazolylmethyl, 4-(2-propyl)oxazolylmethyl, 4-(2-phenyl)oxazolylmethyl, 4-(2-benzyl)oxazolylmethyl, 4-(2-cyclohexyl)oxazolylmethyl, 2-(5-methyl)pyrazinylmethyl, 4-(2,5-dimethyl)thiazolylmethyl, 4-(2-isopropyl-5-methyl)thiazolylmethyl, 4-(2-ethyl-5-methyl)thiazolylmethyl, 4-(2-methyl-5-ethyl)thiazolylmethyl, 4-(2,5-diethyl)thiazolylmethyl, 3-pyridylmethyl or 4-pyridylmethyl.

86. The compound of any of claims 1-85, wherein R⁵ is phenyl, 2-phenylethyl, 3-phenylpropyl, benzyl, 2-methylbenzyl, 3-methylbenzyl, 20 4-methylbenzyl, 2-trifluoromethylbenzyl, 3-trifluoromethylbenzyl, 4-trifluoromethylbenzyl, 2-methoxybenzyl, 3-methoxybenzyl, 4-methoxybenzyl, 4-phenylbenzyl, 1-phenylethyl, 2,4-dimethylbenzyl, 2-fluorobenzyl, 4-fluorobenzyl, 2,4-difluorobenzyl, 4-bromobenzyl, 4-methoxycarbonylbenzyl, 2-chlorobenzyl, 4-chlorobenzyl, 4-methylthiobenzyl, 4-phenoxybenzyl or 4-trifluoromethoxybenzyl.

87. The compound of any of claims 1-86, wherein R⁵ is -N=CR⁶R⁷ where R⁶ and R⁷ are each independently hydrogen, substituted or unsubstituted methyl, substituted or unsubstituted ethyl, substituted or unsubstituted n-propyl, substituted or unsubstituted i-propyl,

-371-

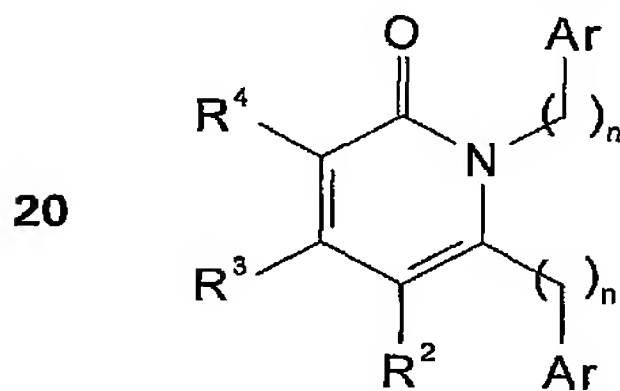
substituted or unsubstituted i-butyl, substituted or unsubstituted tert-butyl, substituted or unsubstituted s-butyl, or substituted or unsubstituted 3-pentyl; where the substituents are selected from one or more Q^1 , with the proviso that R^6 and R^7 are not both methyl.

5 88. The compound of claim 87, wherein R^6 and R^7 are unsubstituted or substituted with one or more Q^1 groups, where Q^1 is hydroxy, halo, alkyl or alkoxy.

 89. The compound of any of claims 87-88, wherein R^6 and R^7 are unsubstituted or substituted with one or more Q^1 groups, where Q^1 is
10 hydroxy, chloro, bromo, methyl or methoxy.

 90. The compound of any of claims 87-89, wherein R^6 and R^7 are each independently hydrogen, methyl, ethyl, isopropyl, n-propyl, s-butyl, 3-pentyl, isobutyl or t-butyl, with the proviso that R^6 and R^7 are not both methyl.

15 91. The compound of any of claims 1-90 that has formula III:

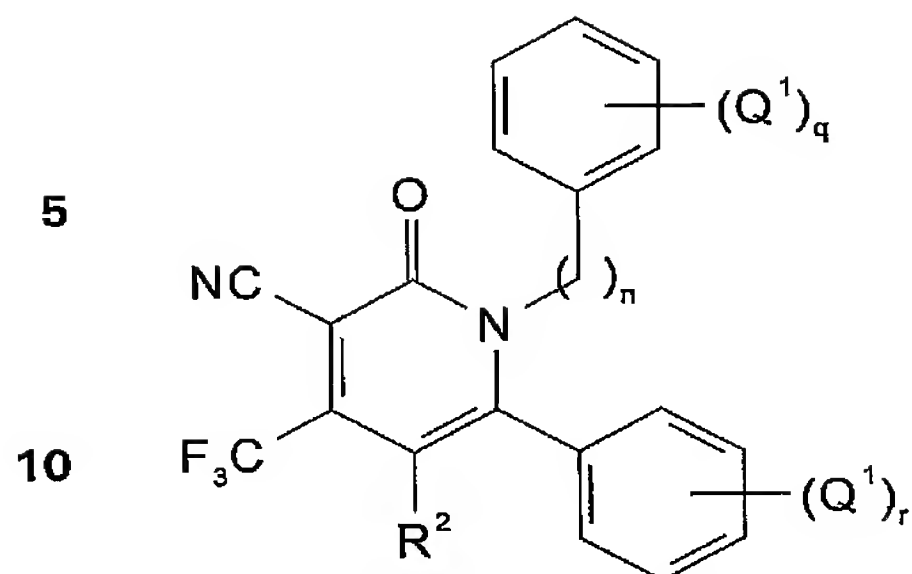


wherein:

each Ar is independently substituted or unsubstituted aryl, substituted or unsubstituted cycloalkyl; substituted or unsubstituted heteroaryl, or substituted or unsubstituted heterocyclyl, where there are
30 0 to 5 substituents each independently selected from Q^1 ; and each n is independently an integer from 0 to 6.

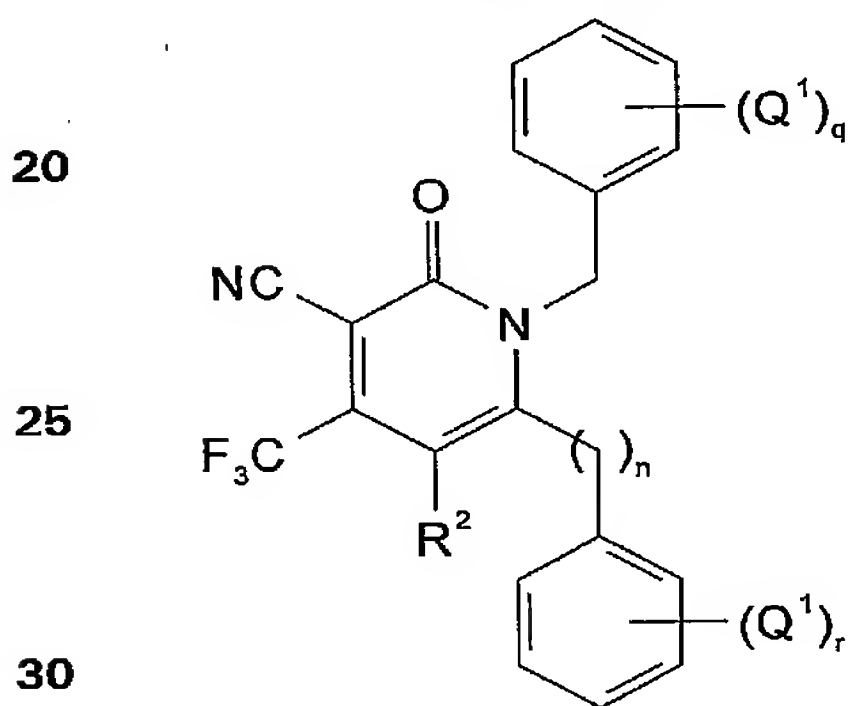
 92. The compound of any of claims 1-91 that has formula IV:

-372-

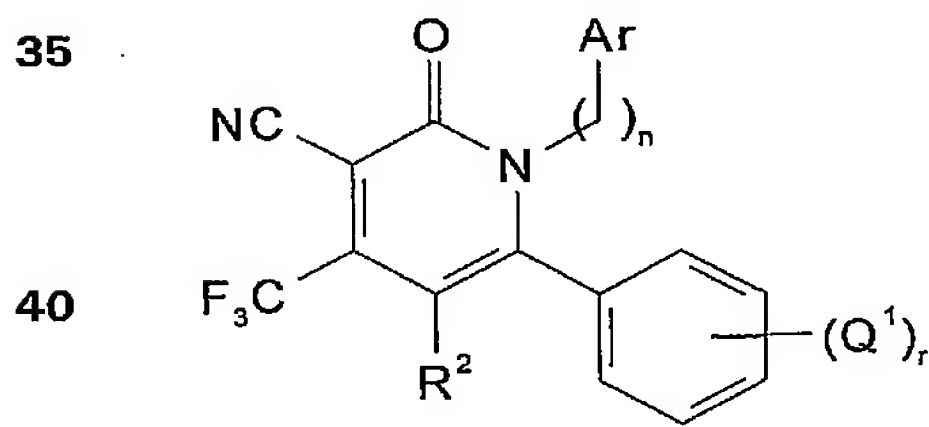


15 wherein q and r are each independently an integer from 0 to 5.

93. The compound of any of claims 1-92 that has formula V:

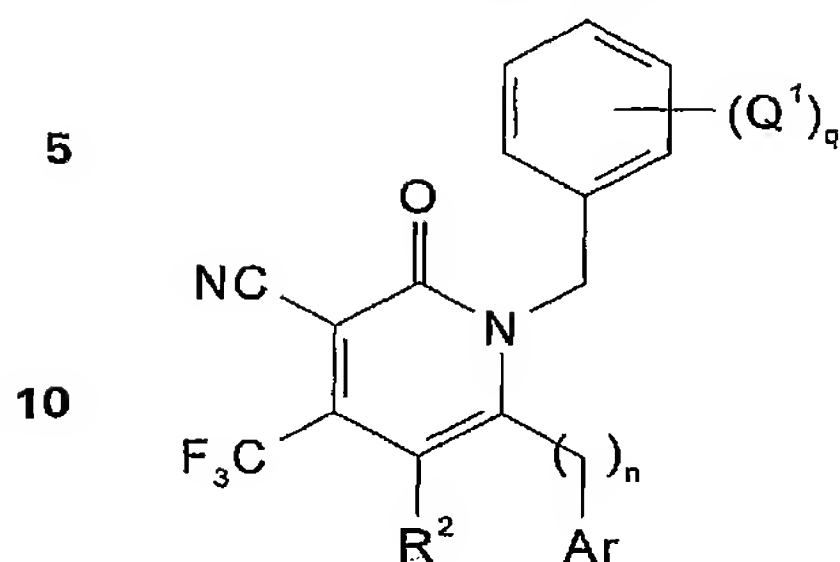


94. The compound of any of claims 1-93 that has formula VI:

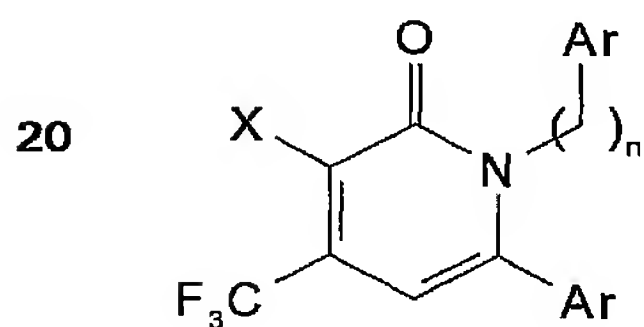


-373-

95. The compound of any of claims 1-94 that has formula VII:

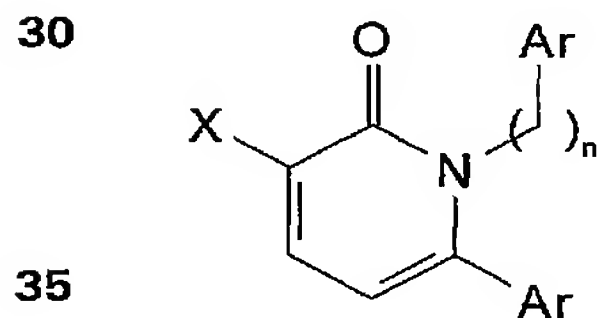


96. The compound of any of claims 1-95 that has formula VIII:



wherein X is cyano, nitro or NR³¹R³².

97. The compound of any of claims 1-96 that has formula IX:

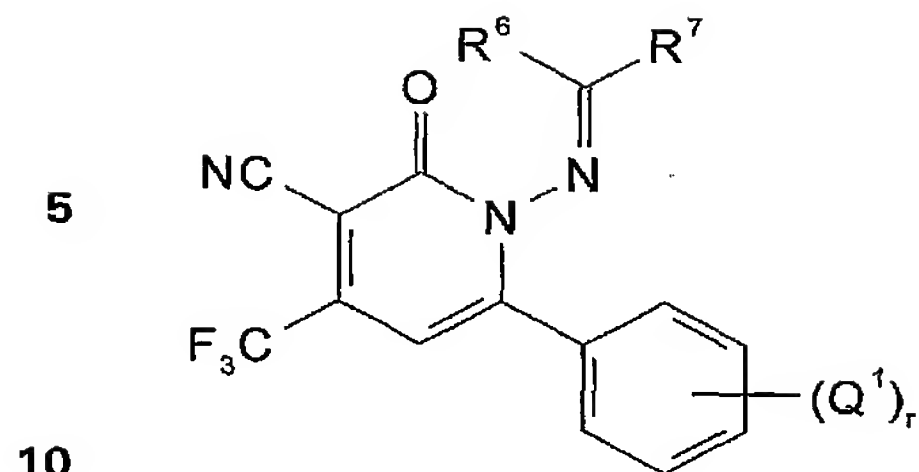


wherein X is bromo, CHO, COOR³⁰ or CONR³¹R³².

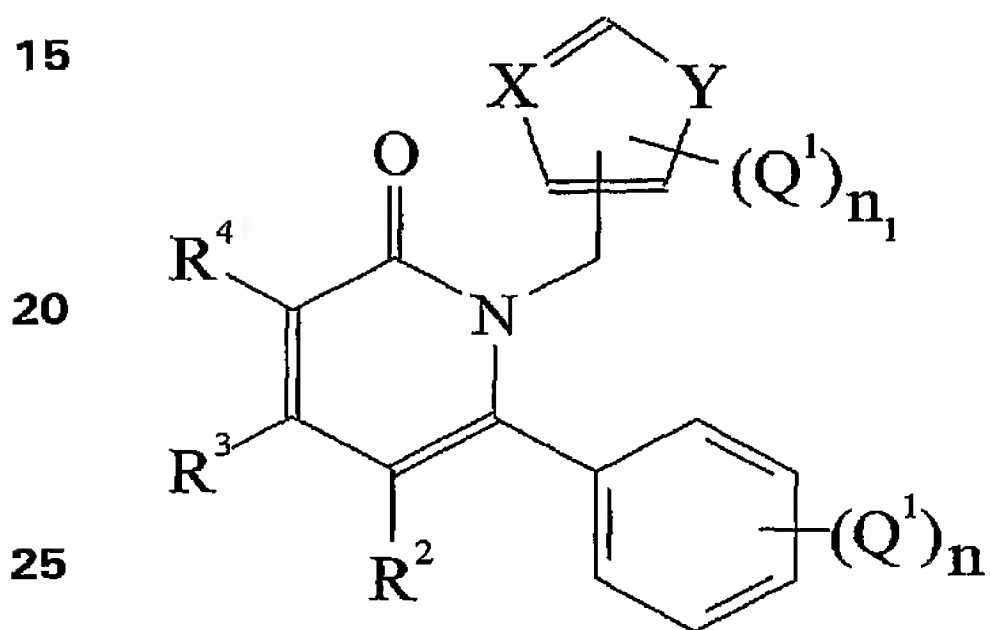
98. The compound of any of claims 1-97 that has formula X:

40

-374-



99. The compound of any of claims 1-98 that has formula XI:



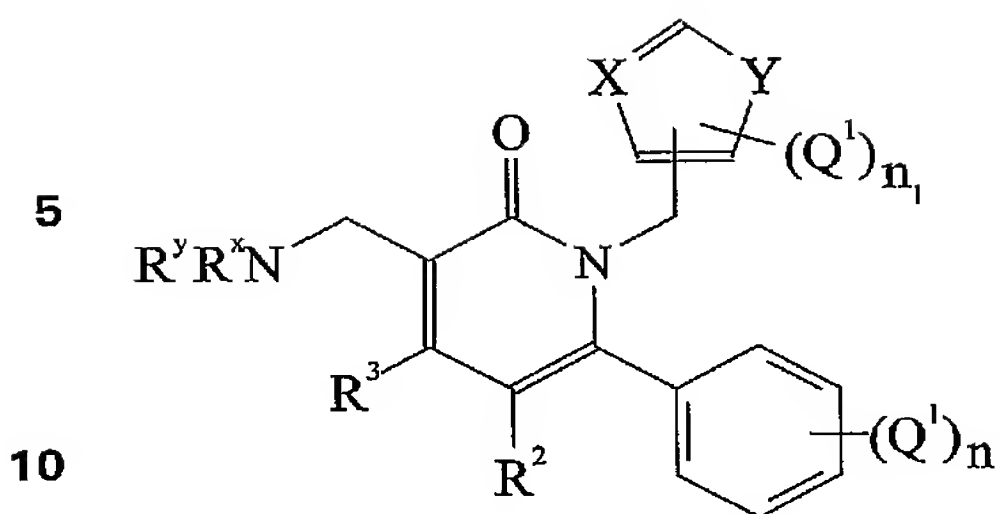
wherein n is an integer from 0 to 5; n_1 is an integer from 0 to 2; Y is selected from $-\text{CH}=\text{CH}-$, $-\text{C}(\text{Q}^1)=\text{CH}-$, $-\text{C}(\text{Q}^1)=\text{C}(\text{Q}^1)-$, $-\text{CH}=\text{N}-$, $-\text{C}(\text{Q}^1)=\text{N}-$, O , S and NR' , where R' is hydrogen, alkyl or aryl and X is N or CH .

100. The compound of any of claims 1-99 that has formula XII:

35

40

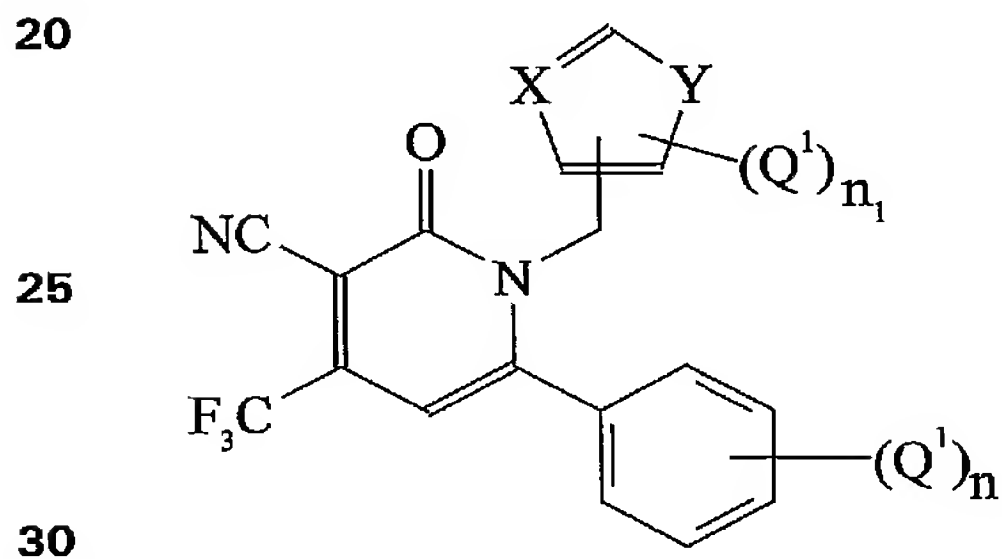
-375-



wherein n is an integer from 0 to 5; n_1 is an integer from 0 to 2; Y is selected from $-\text{CH}=\text{CH}-$, $-\text{C}(\text{Q}^1)=\text{CH}-$, $-\text{C}(\text{Q}^1)=\text{C}(\text{Q}^1)-$, $-\text{CH}=\text{N}-$, -

- 15 $\text{C}(\text{Q}^1)=\text{N}-$, O , S and NR' , where R' is hydrogen, alkyl or aryl and X is N or CH ; R^x and R^y are each independently selected from hydrogen, alkyl, alkylcarbonyl, aryl, arylcarbonyl, aralkylcarbonyl, alkoxycarbonyl, aryloxy carbonyl and aralkoxy carbonyl.

101. The compound of any of claims 1-100 that has formula XIII:

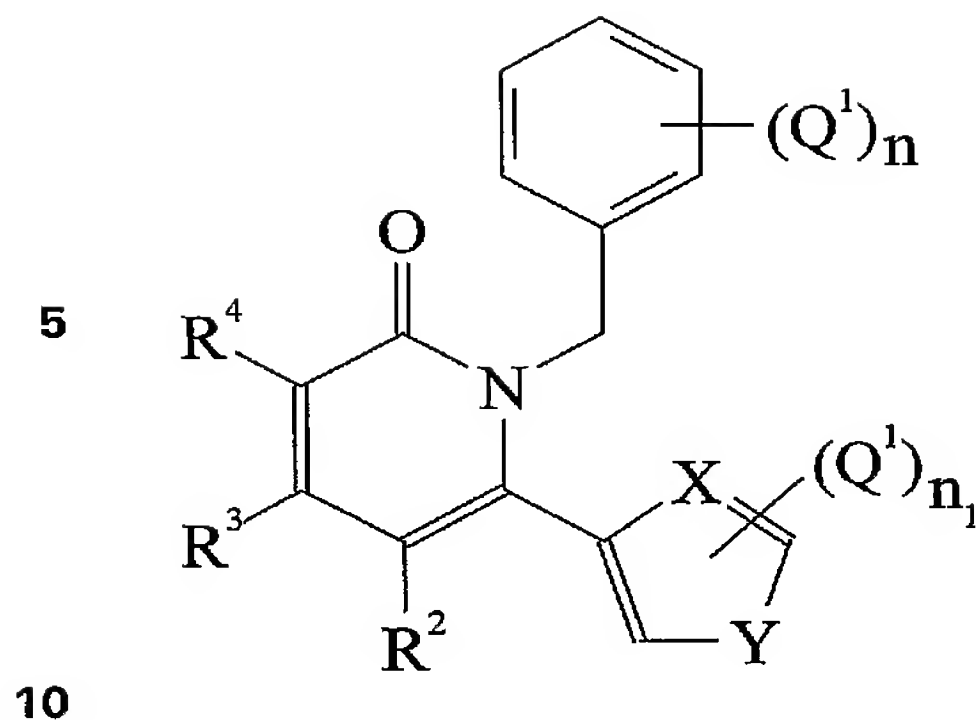


wherein n is an integer from 0 to 5; n_1 is an integer from 0 to 2; Y is selected from $-\text{CH}=\text{CH}-$, $-\text{C}(\text{Q}^1)=\text{CH}-$, $-\text{C}(\text{Q}^1)=\text{C}(\text{Q}^1)-$, $-\text{CH}=\text{N}-$, -

- 35 $\text{C}(\text{Q}^1)=\text{N}-$, O , S and NR' , where R' is hydrogen, alkyl or aryl and X is N or CH .

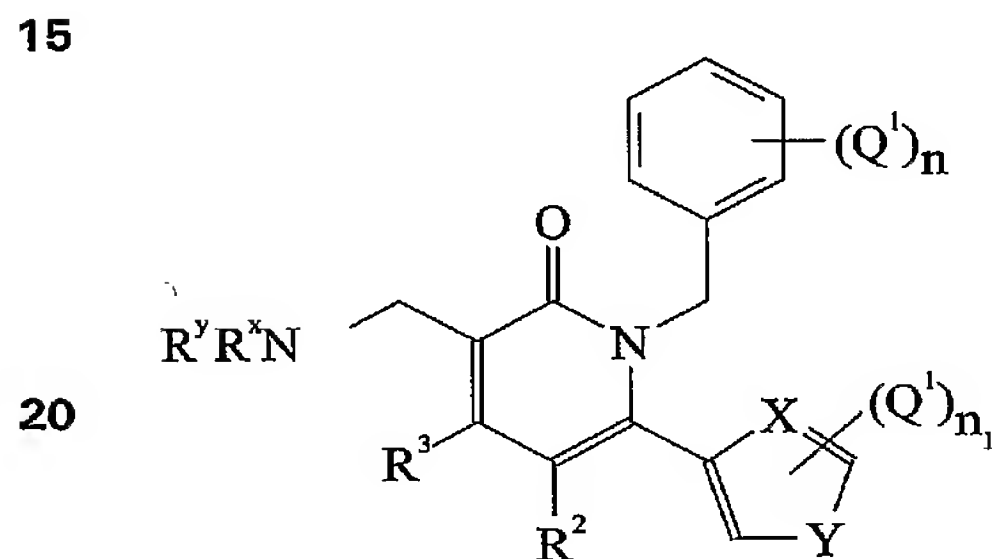
102. The compound of any of claims 1-101 that has formula XIV:

-376-



wherein n is an integer from 0 to 5; n_1 is an integer from 0 to 2; Y is selected from $-\text{CH}=\text{CH}-$, $-\text{C}(\text{Q}^1)=\text{CH}-$, $-\text{C}(\text{Q}^1)=\text{C}(\text{Q}^1)-$, $-\text{CH}=\text{N}-$, $-\text{C}(\text{Q}^1)=\text{N}-$, O , S and NR' , where R' is hydrogen, alkyl or aryl and X is N .

103. The compound of any of claims 1-102 that has formula XV:

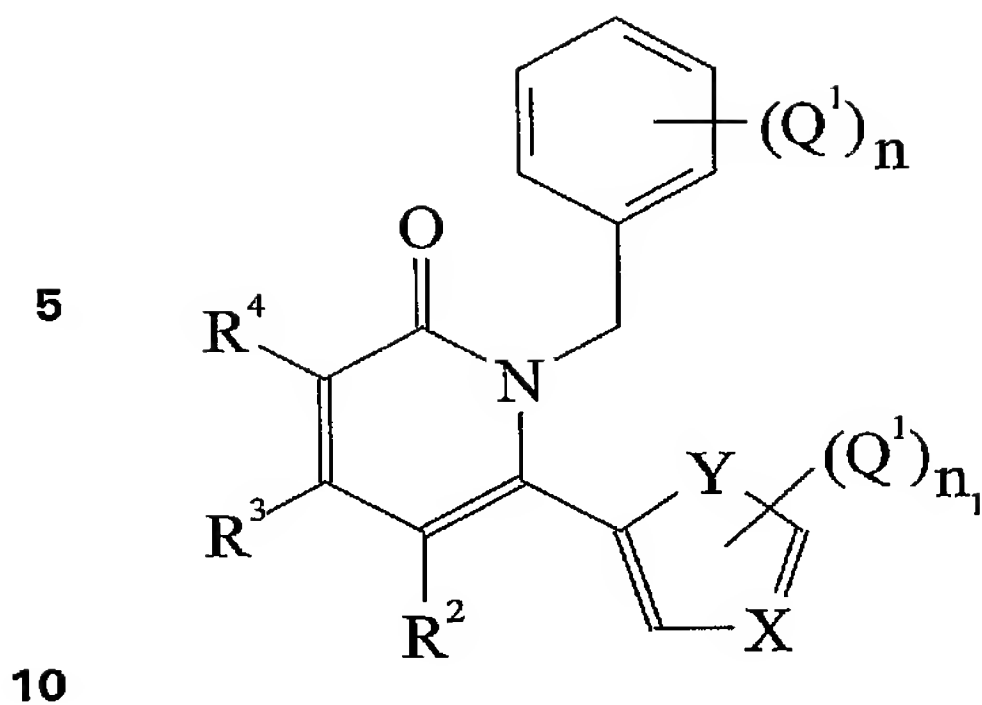


wherein n is an integer from 0 to 5; n_1 is an integer from 0 to 2; Y is selected from $-\text{CH}=\text{CH}-$, $-\text{C}(\text{Q}^1)=\text{CH}-$, $-\text{C}(\text{Q}^1)=\text{C}(\text{Q}^1)-$, $-\text{CH}=\text{N}-$, $-\text{C}(\text{Q}^1)=\text{N}-$, O , S and NR' , where R' is hydrogen, alkyl or aryl and X is N ;

25 R^x and R^y are each independently selected from hydrogen, alkyl, alkylcarbonyl, aryl, arylcarbonyl, aralkylcarbonyl, alkoxycarbonyl, aryloxy carbonyl and aralkoxy carbonyl.

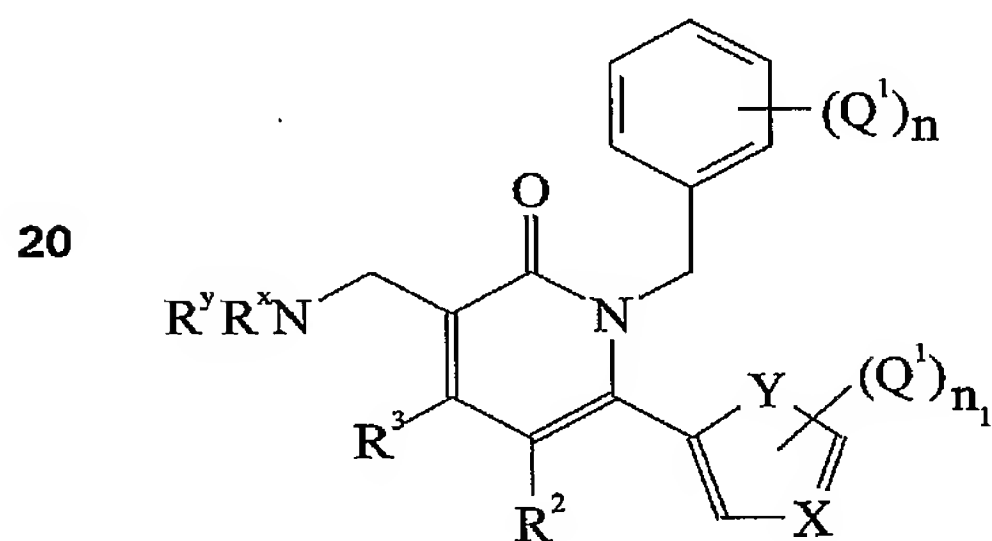
104. The compound of any of claims 1-103 that has formula XVI:

-377-



wherein n is an integer from 0 to 5; n_1 is an integer from 0 to 2; Y is selected from $-\text{CH}=\text{CH}-$, $-\text{C}(\text{Q}^1)=\text{CH}-$, $-\text{C}(\text{Q}^1)=\text{C}(\text{Q}^1)-$, $-\text{CH}=\text{N}-$, $-\text{C}(\text{Q}^1)=\text{N}-$, O , S and NR' , where R' is hydrogen, alkyl or aryl and X is N .

15 105. The compound of any of claims 1-104 that has formula XVI1:

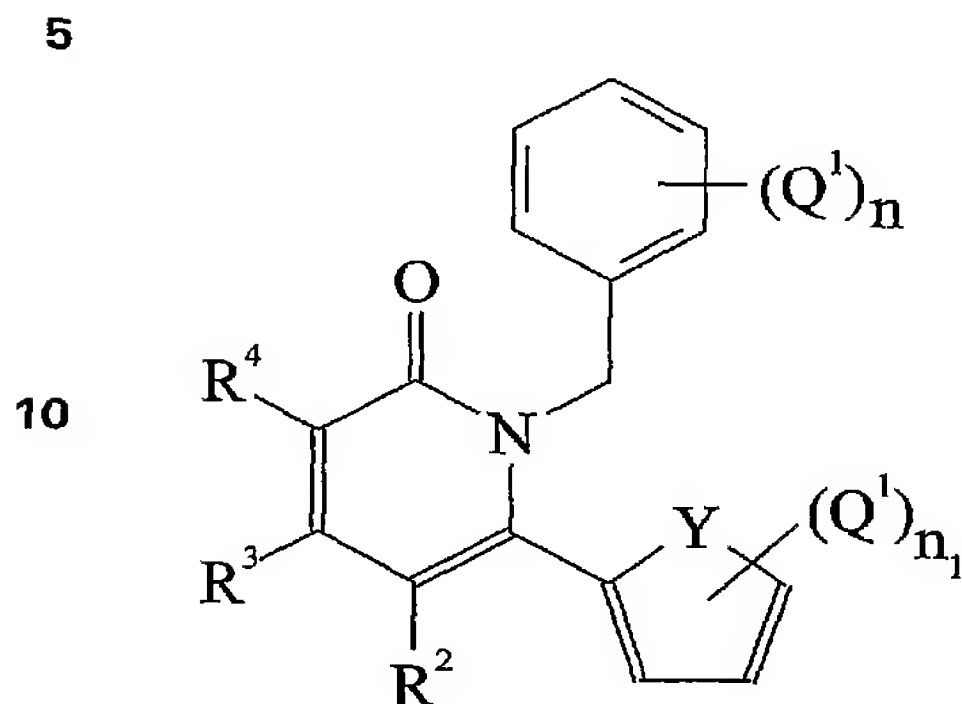


wherein n is an integer from 0 to 5; n_1 is an integer from 0 to 2; Y is selected from $-\text{CH}=\text{CH}-$, $-\text{C}(\text{Q}^1)=\text{CH}-$, $-\text{C}(\text{Q}^1)=\text{C}(\text{Q}^1)-$, $-\text{CH}=\text{N}-$, $-\text{C}(\text{Q}^1)=\text{N}-$, O , S and NR' , where R' is hydrogen, alkyl or aryl and X is N ; R^x and R^y are each independently selected from hydrogen, alkyl,

-378-

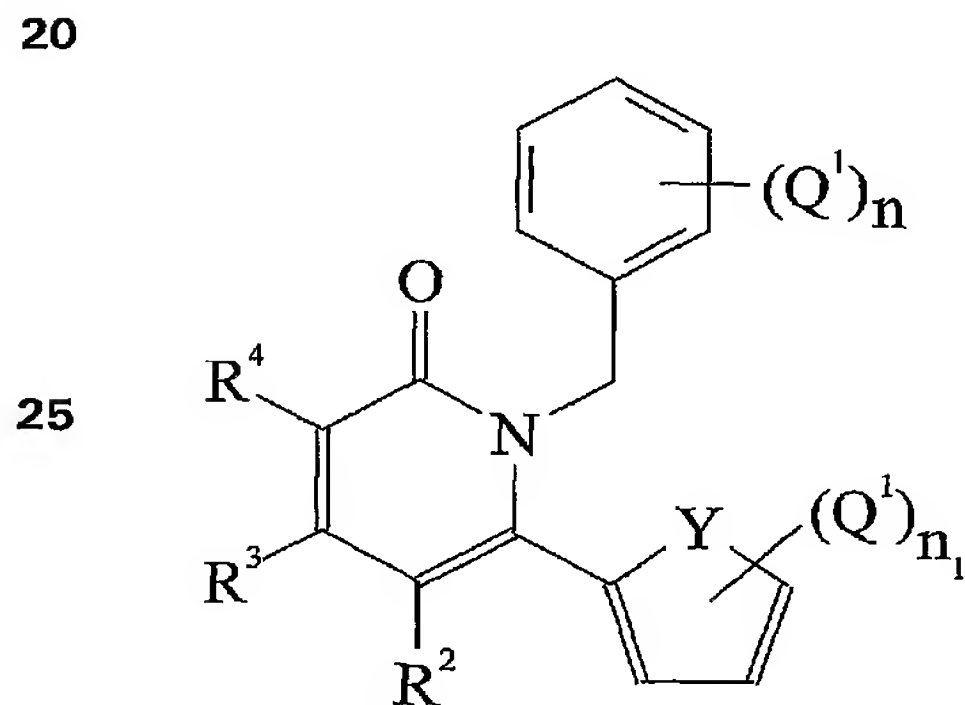
alkylcarbonyl, aryl, arylcarbonyl, aralkylcarbonyl, alkoxy carbonyl, aryloxy carbonyl and aralkoxy carbonyl.

106. The compound of any of claims 1-105 that has formula XVII:



wherein n is an integer from 0 to 5; n_1 is an integer from 0 to 2; Y is selected from O, S and NR' , where R' is hydrogen, alkyl or aryl.

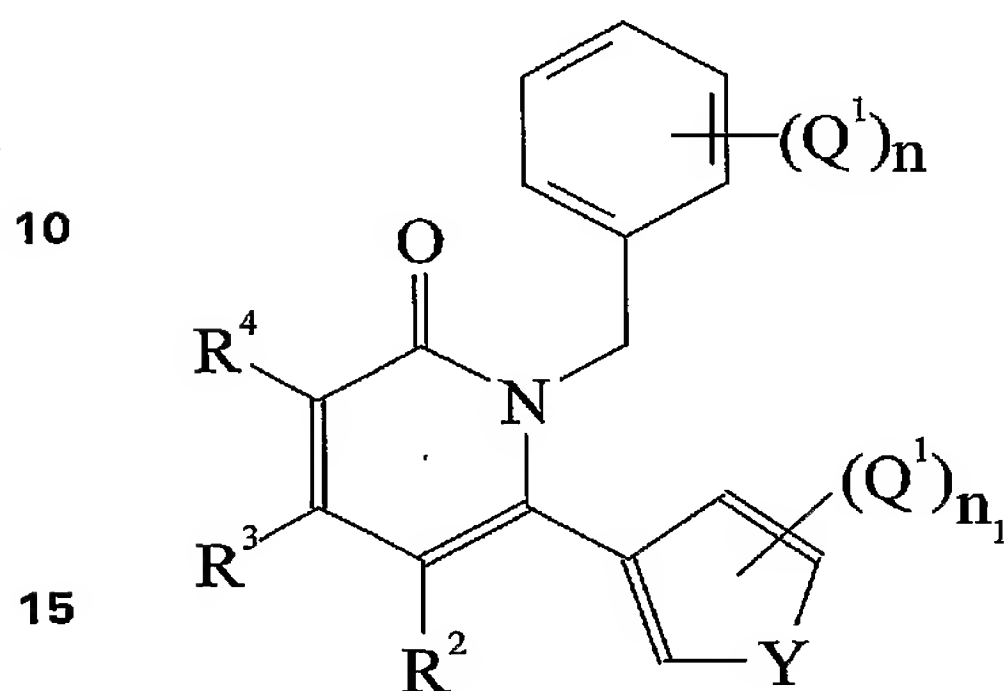
107. The compound of any of claims 1-106 that has formula XVIII:



-379-

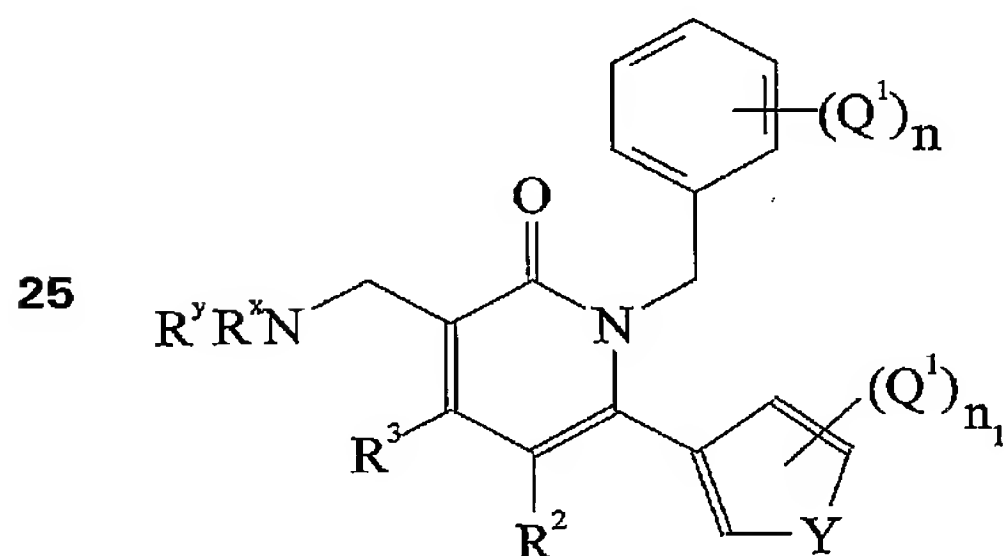
wherein n is an integer from 0 to 5; n_1 is an integer from 0 to 2; Y is selected from O, S and NR' , where R' is hydrogen, alkyl or aryl; R^x and R^y are each independently selected from hydrogen, alkyl, alkylcarbonyl, aryl, arylcarbonyl, aralkylcarbonyl, alkoxycarbonyl, aryloxycarbonyl and aralkoxycarbonyl.

108. The compound of any of claims 1-107 that has formula XIX:



wherein n is an integer from 0 to 5; n_1 is an integer from 0 to 2; Y is selected from O, S and NR' , where R' is hydrogen, alkyl or aryl.

20 109. The compound of any of claims 1-108 that has formula XX:



-380-

wherein n is an integer from 0 to 5; n_1 is an integer from 0 to 2; Y is selected from O, S and NR' , where R' is hydrogen, alkyl or aryl.

110. A compound of any of claims 1-109 selected from Figure 1.

111. A pharmaceutical composition, comprising the compound of
5 any of claims 1-110, or a pharmaceutically acceptable derivative thereof, in a pharmaceutically acceptable carrier.

112. The pharmaceutical composition of claim 111 formulated for single dosage administration.

113. An article of manufacture, comprising packaging material, a
10 compound of any of claims 1-110, or a pharmaceutically acceptable derivative thereof, which is effective for modulating the activity of a nuclear receptor or for treatment, prevention or amelioration of one or more symptoms of nuclear receptor mediated diseases or disorders, or diseases or disorders in which nuclear receptor activity is implicated,
15 within the packaging material, and a label that indicates that the compound or pharmaceutically acceptable derivative thereof is used for modulating the activity of a nuclear receptor or for treatment, prevention or amelioration of one or more symptoms of nuclear receptor mediated diseases or disorders, or diseases or disorders in which nuclear receptor
20 activity is implicated.

114. A method of treating, preventing, or ameliorating the symptoms of a disease or disorder that is modulated or otherwise affected by nuclear receptor activity or in which nuclear receptor activity is implicated, comprising administering to a subject in need thereof an
25 effective amount of a compound of any of claims 1-110, or a pharmaceutically acceptable derivative thereof.

115. The method of claim 114, wherein the disease or disorder is selected from hypercholesterolemia, hyperlipoproteinemia, hypertriglyceridemia, lipodystrophy, hyperglycemia, diabetes mellitus,

-381-

dyslipidemia, atherosclerosis, gallstone disease, acne vulgaris, acneiform skin conditions, diabetes, Parkinson's disease, cancer, Alzheimer's disease, inflammation, immunological disorders, lipid disorders, obesity, conditions characterized by a perturbed epidermal barrier function,
5 conditions of disturbed differentiation or excess proliferation of the epidermis or mucous membrane, and cardiovascular disorders.

116. A method of reducing cholesterol levels in a subject in need thereof, comprising administering an effective amount of a compound of any of claim 1-110 , or a pharmaceutically acceptable derivative thereof.

10 117. A method of treating, preventing, or ameliorating one or more symptoms of a disease or disorder which is affected by cholesterol, triglyceride, or bile acid levels, comprising administering to a subject in need thereof an effective amount of a compound of any of claims 1-110 , or a pharmaceutically acceptable derivative thereof.

15 118. A method of modulating nuclear receptor activity, comprising contacting the nuclear receptor with a compound of any of claims 1-110 , or a pharmaceutically acceptable derivative thereof.

119. The method of claim 118, wherein the nuclear receptor is an orphan nuclear receptor.

20 120. The method of claim 118, wherein the nuclear receptor is liver X receptor (LXR α or LXR β).

121. A method of modulating cholesterol metabolism, comprising administering an effective amount of a compound of any of claims 1-110 , or a pharmaceutically acceptable derivative thereof.

25 122. A method of treating, preventing or ameliorating one or more symptoms of hypocholesterolemia in a subject in need thereof, comprising administering an effective amount of a compound of any of claims 1-110 , or a pharmaceutically acceptable derivative thereof.

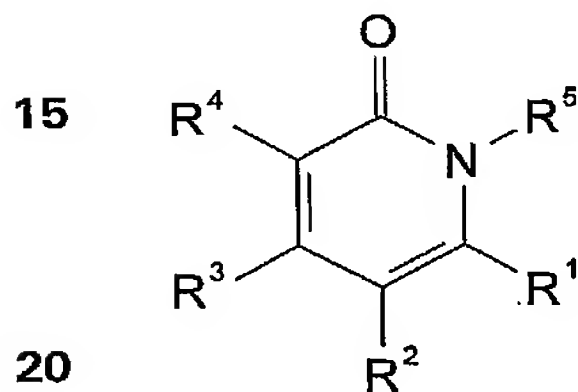
-382-

123. A method of increasing cholesterol efflux from cells of a subject, comprising administering an effective amount of a compound of any of claims 1-110, or a pharmaceutically acceptable derivative thereof.

124. A method of increasing the expression of ATP-Binding
5 Cassette (ABC1) in the cells of a subject, comprising administering an effective amount of a compound of any of claims 1-110 , or a pharmaceutically acceptable derivative thereof.

125. An *in vitro* method for altering nuclear receptor activity, comprising contacting the nuclear receptor with a compound of any of
10 claims 1-110 , or a pharmaceutically acceptable derivative thereof.

126. An article of manufacture, comprising packaging material, a compound of formula I:



or a pharmaceutically acceptable derivative thereof, wherein:

R¹ is selected from substituted or unsubstituted alkyl, substituted
25 or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted aralkyl, substituted or unsubstituted heteroaralkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted cycloalkenyl, substituted or unsubstituted cycloalkynyl, substituted or
30 unsubstituted heterocyclyl, substituted or unsubstituted cycloalkylalkyl and substituted or unsubstituted heterocyclylalkyl;

-383-

R^2 is hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted aryl;

R^3 and R^4 are selected from (i) and (ii) as follows:

- 5 (i) R^3 is substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted alkylaminocarbonyl or $C(J)OR^{30}$; and R^4 is hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, halide, pseudohalide, hydroxycarbonyl, $C(J)R^{30}$, $C(J)NR^{31}R^{32}$, $CH_2NR^{31}R^{32}$, CH_2OR^{31} , $CR^{30}=CR^{31}R^{32}$, NO_2 or $NR^{31}R^{32}$; and
- 10

(ii) R^3 and R^4 , together with the atoms to which they are attached, form a substituted or unsubstituted heterocyclic ring.

- 15 R^5 is substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted aralkyl, substituted or unsubstituted aralkenyl, substituted or unsubstituted aralkynyl, substituted or unsubstituted heteroaralkyl, substituted or unsubstituted heteroaralkenyl, substituted or unsubstituted heteroaralkynyl, $-N=CR^6R^7$ or $-NR^9R^{10}$;
- 20

- R^6 and R^7 are each independently hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted aralkyl, or substituted or unsubstituted heteroaralkyl; or together form substituted or unsubstituted alkylene, substituted or unsubstituted
- 25

-384-

alkenylene, substituted or unsubstituted alkynylene, or $-(CH_2)_xX(CH_2)_y-$ where x and y are each independently 1, 2 or 3, and X is O, S or NR^8 ;

R^8 is substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted alkylcarbonyl, substituted or unsubstituted arylcarbonyl, or substituted or unsubstituted heteroarylcarbonyl;

R^9 and R^{10} are each independently hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted aralkyl, or substituted or unsubstituted heteroaralkyl;

R^{30} is hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted cycloalkylalkyl, substituted or unsubstituted heterocyclalkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted aralkyl, or substituted or unsubstituted heteroaralkyl;

R^{31} and R^{32} are each independently hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted cycloalkylalkyl, substituted or unsubstituted heterocyclalkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted aralkyl, substituted or unsubstituted heteroaralkyl, or $C(J)R^{35}$; or R^{31} and R^{32} , together with the atoms to which they are attached, form substituted or unsubstituted cycloalkyl ring, a substituted or unsubstituted heterocyclic ring or a substituted or unsubstituted heteroaryl;

-385-

J is O, S or NR^{40} ;

R^{35} is hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocyclyl, .

5 substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted alkoxy, substituted or unsubstituted aralkoxy, substituted or unsubstituted alkylamino, substituted or unsubstituted dialkylamino, substituted or unsubstituted arylalkylamino, or substituted or unsubstituted diarylamino;

10 R^{40} is hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl;

where the alkyl, alkenyl, alkynyl, cycloalkyl, heterocyclyl, alkylene, alkenylene, alkynylene, aryl, heteroaryl, aralkyl, aralkenyl, aralkynyl, heteroaralkyl, heteroaralkenyl and heteroaralkynyl moieties of R^1 , R^2 , R^3 ,
 15 R^5 , R^6 , R^7 , R^8 , R^9 and R^{10} are unsubstituted or substituted with one or more substituents, in one embodiment one to three or four substituents, each independently selected from Q^1 , where Q^1 is halo, pseudohalo, hydroxy, oxo, thia, nitrile, nitro, formyl, mercapto, amino, hydroxyalkyl, hydroxyalkylaryloxy, hydroxyaryl, hydroxyalkylaryl, hydroxycarbonyl,
 20 hydroxycarbonylalkyl, alkyl, haloalkyl, polyhaloalkyl, aminoalkyl, diaminoalkyl, alkenyl containing 1 to 2 double bonds, alkynyl containing 1 to 2 triple bonds, cycloalkyl, cycloalkylalkyl, heterocyclyl, heterocyclylalkyl, aryl, diaryl, hydroxyaryl, alkylaryl, heteroaryl, aralkyl, aralkenyl, aralkynyl, alkylaralkyl, heteroarylalkyl, trialkylsilyl,
 25 dialkylarylsilyl, alkyl diarylsilyl, triarylsilyl, alkylidene, arylalkylidene, alkylcarbonyl, alkylarylcarbonyl, arylcarbonyl, heterocyclylcarbonyl, heteroarylcarbonyl, alkoxycarbonyl, alkoxycarbonylalkyl, alkoxycarbonylaryloxy, aryloxycarbonyl, aryloxycarbonylalkyl, heterocyclylcarbonylalkylaryl, aralkoxycarbonyl, aralkoxycarbonylalkyl,

-386-

- arylcarbonylalkyl, aminocarbonyl, alkylaminocarbonyl, dialkylaminocarbonyl, arylaminocarbonyl, diarylaminocarbonyl, arylalkylaminocarbonyl, alkoxy, aryloxy, haloalkoxy, alkoxyaryloxy, alkylaryloxy, diaryloxy, alkylaryloxyalkyl, alkyl diaryloxy, perfluoroalkoxy, alkenyloxy, alkynyloxy, aryloxyalkoxy, aralkoxyaryloxy, alkylarylcyloalkyloxy, heterocycloxy, alkoxyalkyl, alkoxyalkoxyalkyl, alkylheteroaryloxy, alkylcyloalkoxy, cycloalkyloxy, heterocyclyloxy, aralkoxy, haloaryloxy, heteroaryloxy, alkylheteroaryloxy, alkoxycarbonylheterocycloxy, alkylcarbonylaryloxy, alkylcarbonyloxy, arylcarbonyloxy, aralkylcarbonyloxy, alkoxycarbonyloxy, aryloxy carbonyloxy, alkoxyaryloxy, aralkoxycarbonyloxy, ureido, alkylureido, arylureido, amino, aminoalkyl, alkylaminoalkyl, dialkylaminoalkyl, arylaminoalkyl, diarylaminoalkyl, alkylarylaminominoalkyl, alkylamino, dialkylamino, haloalkylamino, haloalkylarylaminomino, arylamino, diarylamino, alkylamino, aralkylamino, alkylcarbonylamino, aralkylcarbonylamino, haloalkylcarbonylamino, alkoxycarbonylamino, aralkoxycarbonylamino, arylcarbonylamino, arylcarbonylaminoalkyl, aryloxy carbonylaminoalkyl, aryloxyarylcarbonylamino, aryloxy carbonylamino, alkylenedioxyalkyl, dialkylalkylenedioxyalkyl, alkylsulfonylamino, arylsulfonylamino, azido, dialkylphosphonyl, alkylarylphosphonyl, diarylphosphonyl, alkylthio, arylthio, perfluoroalkylthio, hydroxycarbonylalkylthio, thiocyno, isothiocyno, alkylsulfinyl, alkylsulfonyl, arylsulfinyl, arylsulfonyl, aminosulfonyl, alkylaminosulfonyl, dialkylaminosulfonyl, arylaminosulfonyl, diarylamino sulfonyl or alkylarylaminosulfonyl; or two Q¹ groups, which substitute atoms in a 1,2 or 1,3 arrangement, together form alkylenedioxy (*i.e.*, -O-(CH₂)_z-O-), thioalkylenoxy (*i.e.*, -S-(CH₂)_z-O-) or alkylenedithioxy (*i.e.*, -S-(CH₂)_z-S-) where z is 1 or 2; and each Q¹ is independently unsubstituted or substituted with one or more substituents, in one embodiment one to three or four substituents,

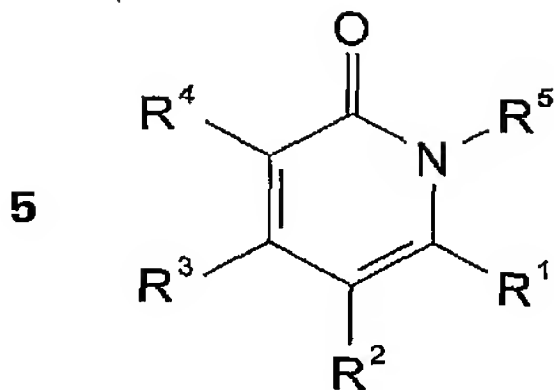
-387-

each independently selected from Q^2 , where Q^2 is halo, pseudohalo, hydroxy, oxo, thia, nitrile, nitro, formyl, mercapto, amino, hydroxyalkyl, hydroxyaryl, hydroxycarbonyl, alkyl, haloalkyl, polyhaloalkyl, aminoalkyl, diaminoalkyl, alkenyl containing 1 to 2 double bonds, alkynyl containing
5 1 to 2 triple bonds, cycloalkyl, heterocyclyl, aryl, heteroaryl, aralkyl, aralkenyl, aralkynyl, alkoxycarbonyl, aryloxycarbonyl, aralkoxycarbonyl, arylcarbonylalkyl, aminocarbonyl, alkoxy, aryloxy, aralkoxy, alkylenedioxy, amino, aminoalkyl, dialkylamino, arylamino, diarylamino, alkylamino, dialkylamino, haloalkylamino, arylamino, diarylamino, alkyl-
10 arylamino, aralkylamino, alkoxycarbonylamino, arylcarbonylamino, alkylthio or arylthio;

which is effective for modulating the activity of a nuclear receptor or for treatment, prevention or amelioration of one or more symptoms of nuclear receptor mediated diseases or disorders, or diseases or disorders
15 in which nuclear receptor activity is implicated, within the packaging material, and a label that indicates that the compound or pharmaceutically acceptable derivative thereof is used for modulating the activity of a nuclear receptor or for treatment, prevention or amelioration of one or more symptoms of nuclear receptor mediated diseases or
20 disorders, or diseases or disorders in which nuclear receptor activity is implicated.

127. A method of treating, preventing, or ameliorating the symptoms of a disease or disorder that is modulated or otherwise affected by nuclear receptor activity or in which nuclear receptor activity
25 is implicated, comprising administering to a subject in need thereof an effective amount of a compound of formula I:

-388-



or a pharmaceutically acceptable derivative thereof, wherein:

R^1 is selected from substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted aralkyl, substituted or unsubstituted heteroaralkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted cycloalkenyl, substituted or unsubstituted cycloalkynyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted cycloalkylalkyl and substituted or unsubstituted heterocyclylalkyl;

R^2 is hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted aryl;

R^3 and R^4 are selected from (i) and (ii) as follows:

(i) R^3 is substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted alkylaminocarbonyl or $C(J)OR^{30}$; and R^4 is hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, halide, pseudohalide, hydroxycarbonyl, $C(J)R^{30}$, $C(J)NR^{31}R^{32}$, $CH_2NR^{31}R^{32}$, CH_2OR^{31} , $CR^{30} = CR^{31}R^{32}$, NO_2 or $NR^{31}R^{32}$; and

-389-

(ii) R^3 and R^4 , together with the atoms to which they are attached, form a substituted or unsubstituted heterocyclic ring;

R^5 is substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted aralkyl, substituted or unsubstituted aralkenyl, substituted or unsubstituted aralkynyl, substituted or unsubstituted heteroaralkyl, substituted or unsubstituted heteroaralkenyl, substituted or unsubstituted heteroaralkynyl, $-N=CR^6R^7$ or $-NR^9R^{10}$;

R^6 and R^7 are each independently hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted aralkyl, or substituted or unsubstituted heteroaralkyl; or together form substituted or unsubstituted alkylene, substituted or unsubstituted alkenylene, substituted or unsubstituted alkynylene, or $-(CH_2)_xX(CH_2)_y-$ where x and y are each independently 1, 2 or 3, and X is O, S or NR^8 ;

R^8 is substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted alkylcarbonyl, substituted or unsubstituted arylcarbonyl, or substituted or unsubstituted heteroarylcarbonyl;

R^9 and R^{10} are each independently hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted aralkyl, or substituted or unsubstituted heteroaralkyl;

-390-

R^{30} is hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted cycloalkylalkyl, substituted or unsubstituted heterocyclalkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted aralkyl, or substituted or unsubstituted heteroaralkyl;

R^{31} and R^{32} are each independently hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted cycloalkylalkyl, substituted or unsubstituted heterocyclalkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted aralkyl, substituted or unsubstituted heteroaralkyl, or $C(J)R^{35}$; or R^{31} and R^{32} , together with the atoms to which they are attached, form substituted or unsubstituted cycloalkyl ring, a substituted or unsubstituted heterocyclic ring or a substituted or unsubstituted heteroaryl ring;

J is O, S or NR^{40} ;

R^{35} is hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted alkoxy, substituted or unsubstituted aralkoxy, substituted or unsubstituted alkylamino, substituted or unsubstituted dialkylamino, substituted or unsubstituted arylalkylamino, or substituted or unsubstituted diarylamino;

R^{40} is hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl;

-391-

where the alkyl, alkenyl, alkynyl, cycloalkyl, heterocyclyl, alkylene, alkenylene, alkynylene, aryl, heteroaryl, aralkyl, aralkenyl, aralkynyl, heteroaralkyl, heteroaralkenyl and heteroaralkynyl moieties of R¹, R², R³, R⁵, R⁶, R⁷, R⁸, R⁹ and R¹⁰ are unsubstituted or substituted with one or

5 more substituents, in one embodiment one to three or four substituents, each independently selected from Q¹, where Q¹ is halo, pseudohalo, hydroxy, oxo, thia, nitrile, nitro, formyl, mercapto, amino, hydroxyalkyl, hydroxyalkylaryloxy, hydroxyaryl, hydroxyalkylaryl, hydroxycarbonyl, hydroxycarbonylalkyl, alkyl, haloalkyl, polyhaloalkyl, aminoalkyl,

10 diaminoalkyl, alkenyl containing 1 to 2 double bonds, alkynyl containing 1 to 2 triple bonds, cycloalkyl, cycloalkylalkyl, heterocyclyl, heterocyclylalkyl, aryl, diaryl, hydroxyaryl, alkylaryl, heteroaryl, aralkyl, aralkenyl, aralkynyl, alkylaralkyl, heteroarylalkyl, trialkylsilyl, dialkylarylsilyl, alkyl diarylsilyl, triarylsilyl, alkylidene, arylalkylidene,

15 alkylcarbonyl, alkylarylcarbonyl, arylcarbonyl, heterocyclylcarbonyl, heteroarylcarbonyl, alkoxycarbonyl, alkoxycarbonylalkyl, alkoxycarbonylaryloxy, aryloxycarbonyl, aryloxycarbonylalkyl, heterocyclylcarbonylalkylaryl, aralkoxycarbonyl, aralkoxycarbonylalkyl, arylcarbonylalkyl, aminocarbonyl, alkylaminocarbonyl,

20 dialkylaminocarbonyl, arylaminocarbonyl, diarylaminocarbonyl, arylalkylaminocarbonyl, alkoxy, aryloxy, haloalkoxy, alkoxyaryloxy, alkylaryloxy, diaryloxy, alkylaryloxyalkyl, alkyl diaryloxy, perfluoroalkoxy, alkenyloxy, alkynyloxy, aryloxyalkoxy, aralkoxyaryloxy, alkylarylcycloalkyloxy, heterocycloxy, alkoxyalkyl, alkoxyalkoxyalkyl,

25 alkylheteroaryloxy, alkylcycloalkoxy, cycloalkyloxy, heterocycliloxy, aralkoxy, haloaryloxy, heteroaryloxy, alkylheteroaryloxy, alkoxycarbonylheterocycloxy, alkylcarbonylaryloxy, alkylcarbonyloxy, arylcarbonyloxy, aralkylcarbonyloxy, alkoxycarbonyloxy, aryloxycarbonyloxy, alkoxyaryloxy, aralkoxycarbonyloxy, ureido, alkylureido, aryl-

-392-

ureido, amino, aminoalkyl, alkylaminoalkyl, dialkylaminoalkyl, aryl-aminoalkyl, diarylaminoalkyl, alkylarylaminoalkyl, alkylamino, dialkyl-amino, haloalkylamino, haloalkylarylamino, arylamino, diarylamino, alkyl-arylamino, aralkylamino, alkylcarbonylamino, aralkylcarbonylamino,

5 haloalkylcarbonylamino, alkoxycarbonylamino, aralkoxycarbonylamino, arylcarbonylamino, arylcarbonylaminoalkyl, aryloxycarbonylaminoalkyl, aryloxyarylcabonylamino, aryloxycarbonylamino, alkylenedioxyalkyl, dialkylalkylenedioxyalkyl, alkylsulfonylamino, arylsulfonylamino, azido, dialkylphosphonyl, alkylarylphosphonyl, diarylphosphonyl, alkylthio, aryl-

10 thio, perfluoroalkylthio, hydroxycarbonylalkylthio, thiocyano, isothiocyano, alkylsulfinyl, alkylsulfonyl, arylsulfinyl, arylsulfonyl, aminosulfonyl, alkylaminosulfonyl, dialkylaminosulfonyl, arylaminosulfonyl, diarylaminosulfonyl or alkylarylaminosulfonyl; or two Q^1 groups, which substitute atoms in a 1,2 or 1,3 arrangement, together

15 form alkylenedioxy (*i.e.*, $-O-(CH_2)_z-O-$), thioalkylenoxy (*i.e.*, $-S-(CH_2)_z-O-$) or alkylenedithioxy (*i.e.*, $-S-(CH_2)_z-S-$) where z is 1 or 2; and each Q^1 is independently unsubstituted or substituted with one or more substituents, in one embodiment one to three or four substituents, each independently selected from Q^2 , where Q^2 is halo, pseudohalo,

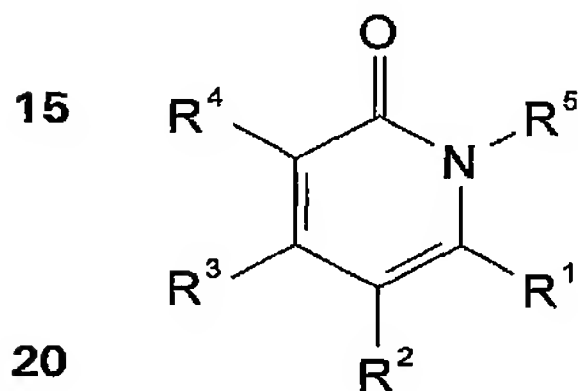
20 hydroxy, oxo, thia, nitrile, nitro, formyl, mercapto, amino, hydroxyalkyl, hydroxyaryl, hydroxycarbonyl, alkyl, haloalkyl, polyhaloalkyl, aminoalkyl, diaminoalkyl, alkenyl containing 1 to 2 double bonds, alkynyl containing 1 to 2 triple bonds, cycloalkyl, heterocyclyl, aryl, heteroaryl, aralkyl, aralkenyl, aralkynyl, alkoxycarbonyl, aryloxycarbonyl, aralkoxycarbonyl,

25 arylcarbonylalkyl, aminocarbonyl, alkoxy, aryloxy, aralkoxy, alkylenedioxy, amino, aminoalkyl, dialkylamino, arylamino, diarylamino, alkylamino, dialkylamino, haloalkylamino, arylamino, diarylamino, alkyl-arylamino, aralkylamino, alkoxycarbonylamino, arylcarbonylamino, alkylthio or arylthio.

-393-

128. The method of claim 127, wherein the disease or disorder is selected from hypercholesterolemia, hyperlipoproteinemia, hypertriglyceridemia, lipodystrophy, hyperglycemia, diabetes mellitus, dyslipidemia, atherosclerosis, gallstone disease, acne vulgaris, acneiform skin conditions, diabetes, Parkinson's disease, cancer, Alzheimer's disease, inflammation, immunological disorders, lipid disorders, obesity, conditions characterized by a perturbed epidermal barrier function, conditions of disturbed differentiation or excess proliferation of the epidermis or mucous membrane, and cardiovascular disorders.

129. A method of reducing cholesterol levels in a subject in need thereof, comprising administering an effective amount of a compound of formula I:



or a pharmaceutically acceptable derivative thereof, wherein:

R¹ is selected from substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted aralkyl, substituted or unsubstituted heteroaralkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted cycloalkenyl, substituted or unsubstituted cycloalkynyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted cycloalkylalkyl and substituted or unsubstituted heterocyclylalkyl;

-394-

R^2 is hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted aryl;

R^3 and R^4 are selected from (i) and (ii) as follows:

- 5 (i) R^3 is substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted alkylaminocarbonyl or $C(J)OR^{30}$; and R^4 is hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, halide, pseudohalide, hydroxycarbonyl, $C(J)R^{30}$, $C(J)NR^{31}R^{32}$, $CH_2NR^{31}R^{32}$, CH_2OR^{31} , $CR^{30}=CR^{31}R^{32}$, NO_2 or $NR^{31}R^{32}$; and
- 10 (ii) R^3 and R^4 , together with the atoms to which they are attached, form a substituted or unsubstituted heterocyclic ring;
- 15 R^5 is substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted aralkyl, substituted or unsubstituted aralkenyl, substituted or unsubstituted aralkynyl, substituted or unsubstituted heteroaralkyl, substituted or unsubstituted heteroaralkenyl, substituted or unsubstituted heteroaralkynyl, $-N=CR^6R^7$ or $-NR^9R^{10}$;
- 20

- R^6 and R^7 are each independently hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted aralkyl, or substituted or unsubstituted heteroaralkyl; or together form substituted or unsubstituted alkylene, substituted or unsubstituted
- 25

-395-

alkenylene, substituted or unsubstituted alkynylene, or $-(CH_2)_xX(CH_2)_y-$ where x and y are each independently 1, 2 or 3, and X is O, S or NR^8 ;

R^8 is substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted alkylcarbonyl, substituted or unsubstituted arylcarbonyl, or substituted or unsubstituted heteroarylcarbonyl;

R^9 and R^{10} are each independently hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted aralkyl, or substituted or unsubstituted heteroaralkyl;

R^{30} is hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted cycloalkylalkyl, substituted or unsubstituted heterocyclalkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted aralkyl, or substituted or unsubstituted heteroaralkyl;

R^{31} and R^{32} are each independently hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted cycloalkylalkyl, substituted or unsubstituted heterocyclalkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted aralkyl, substituted or unsubstituted heteroaralkyl, or $C(J)R^{35}$; or R^{31} and R^{32} , together with the atoms to which they are attached, form substituted or unsubstituted cycloalkyl ring, a substituted or unsubstituted heterocyclic ring or a substituted or unsubstituted heteroaryl ring;

-396-

J is O, S or NR⁴⁰;

- R³⁵ is hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted alkoxy, substituted or unsubstituted aralkoxy, substituted or unsubstituted alkylamino, substituted or unsubstituted dialkylamino, substituted or unsubstituted arylalkylamino, or substituted or unsubstituted diarylamino;
- 10 R⁴⁰ is hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl;
- where the alkyl, alkenyl, alkynyl, cycloalkyl, heterocyclyl, alkylene, alkenylene, alkynylene, aryl, heteroaryl, aralkyl, aralkenyl, aralkynyl, heteroaralkyl, heteroaralkenyl and heteroaralkynyl moieties of R¹, R², R³, R⁵, R⁶, R⁷, R⁸, R⁹ and R¹⁰ are unsubstituted or substituted with one or more substituents, in one embodiment one to three or four substituents, each independently selected from Q¹, where Q¹ is halo, pseudohalo, hydroxy, oxo, thia, nitrile, nitro, formyl, mercapto, amino, hydroxyalkyl, hydroxyalkylaryloxy, hydroxyaryl, hydroxyalkylaryl, hydroxycarbonyl, hydroxycarbonylalkyl, alkyl, haloalkyl, polyhaloalkyl, aminoalkyl, diaminoalkyl, alkenyl containing 1 to 2 double bonds, alkynyl containing 1 to 2 triple bonds, cycloalkyl, cycloalkylalkyl, heterocyclyl, heterocyclylalkyl, aryl, diaryl, hydroxyaryl, alkylaryl, heteroaryl, aralkyl, aralkenyl, aralkynyl, alkylaralkyl, heteroarylalkyl, trialkylsilyl, dialkylarylsilyl, alkyl diarylsilyl, triarylsilyl, alkylidene, arylalkylidene, alkylcarbonyl, alkylarylcarbonyl, arylcarbonyl, heterocyclylcarbonyl, heteroarylcarbonyl, alkoxycarbonyl, alkoxycarbonylalkyl, alkoxycarbonylaryloxy, aryloxycarbonyl, aryloxycarbonylalkyl, heterocyclylcarbonylalkylaryl, aralkoxycarbonyl, aralkoxycarbonylalkyl,
- 15
- 20
- 25

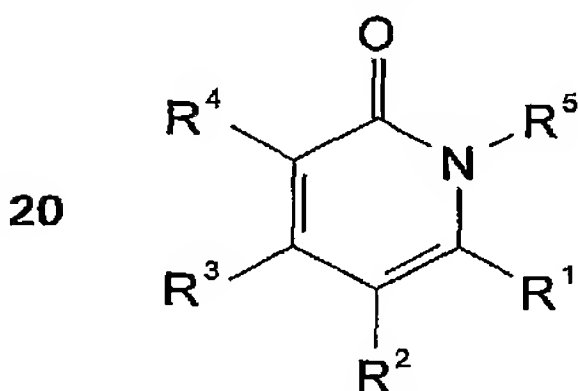
-397-

- arylcarbonylalkyl, aminocarbonyl, alkylaminocarbonyl,
 dialkylaminocarbonyl, arylaminocarbonyl, diarylaminocarbonyl,
 arylalkylaminocarbonyl, alkoxy, aryloxy, haloalkoxy, alkoxyaryloxy,
 alkylaryloxy, diaryloxy, alkylaryloxyalkyl, alkyl diaryloxy, perfluoroalkoxy,
 5 alkenyloxy, alkynyloxy, aryloxyalkoxy, aralkoxyaryloxy,
 alkylaryl cycloalkoxy, heterocycloxy, alkoxyalkyl, alkoxyalkoxyalkyl,
 alkylheteroaryloxy, alkyl cycloalkoxy, cycloalkoxy, heterocycloxy,
 aralkoxy, haloaryloxy, heteroaryloxy, alkylheteroaryloxy,
 alkoxy carbonyl heterocycloxy, alkyl carbonyl aryloxy, alkyl carbonyloxy,
 10 aryl carbonyloxy, aralkyl carbonyloxy, alkoxy carbonyloxy, aryloxy carbonyloxy,
 alkoxyaryloxy, aralkoxy carbonyloxy, ureido, alkylureido, aryl-
 ureido, amino, aminoalkyl, alkylaminoalkyl, dialkylaminoalkyl, aryl-
 aminoalkyl, diarylaminoalkyl, alkylaryl aminoalkyl, alkylamino, dialkyl-
 amino, haloalkylamino, haloalkylaryl amino, arylamino, diarylamino, alkyl-
 15 arylamino, aralkylamino, alkyl carbonylamino, aralkyl carbonylamino,
 haloalkyl carbonylamino, alkoxy carbonylamino, aralkoxy carbonylamino,
 aryl carbonylamino, aryl carbonylaminoalkyl, aryloxy carbonylaminoalkyl,
 aryloxyaryl carbonylamino, aryloxy carbonylamino, alkylenedioxyalkyl,
 dialkylalkylenedioxyalkyl, alkylsulfonylamino, arylsulfonylamino, azido,
 20 dialkylphosphonyl, alkylarylphosphonyl, diarylphosphonyl, alkylthio, aryl-
 thio, perfluoroalkylthio, hydroxy carbonyl alkylthio, thiocyno,
 isothiocyno, alkylsulfinyl, alkylsulfonyl, arylsulfinyl, arylsulfonyl,
 aminosulfonyl, alkylaminosulfonyl, dialkylaminosulfonyl,
 arylaminosulfonyl, diarylamino sulfonyl or alkylaryl aminosulfonyl; or two
 25 Q¹ groups, which substitute atoms in a 1,2 or 1,3 arrangement, together
 form alkylenedioxy (*i.e.*, -O-(CH₂)_z-O-), thioalkylenoxy (*i.e.*,
 -S-(CH₂)_z-O-) or alkylenedithioxy (*i.e.*, -S-(CH₂)_z-S-) where z is 1 or 2; and
 each Q¹ is independently unsubstituted or substituted with one or
 more substituents, in one embodiment one to three or four substituents,

-398-

each independently selected from Q^2 , where Q^2 is halo, pseudohalo, hydroxy, oxo, thia, nitrile, nitro, formyl, mercapto, amino, hydroxyalkyl, hydroxyaryl, hydroxycarbonyl, alkyl, haloalkyl, polyhaloalkyl, aminoalkyl, diaminoalkyl, alkenyl containing 1 to 2 double bonds, alkynyl containing
 5 1 to 2 triple bonds, cycloalkyl, heterocyclyl, aryl, heteroaryl, aralkyl, aralkenyl, aralkynyl, alkoxycarbonyl, aryloxycarbonyl, aralkoxycarbonyl, arylcarbonylalkyl, aminocarbonyl, alkoxy, aryloxy, aralkoxy, alkylenedioxy, amino, aminoalkyl, dialkylamino, arylamino, diarylamino, alkylamino, dialkylamino, haloalkylamino, arylamino, diarylamino, alkyl-
 10 arylamino, aralkylamino, alkoxycarbonylamino, arylcarbonylamino, alkylthio or arylthio.

130. A method of treating, preventing, or ameliorating one or more symptoms of a disease or disorder which is affected by cholesterol, triglyceride, or bile acid levels, comprising administering to a subject in
 15 need thereof an effective amount of a compound of formula I:



or a pharmaceutically acceptable derivative thereof, wherein:

R^1 is selected from substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted aralkyl, substituted or unsubstituted heteroaralkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted cycloalkenyl, substituted or unsubstituted cycloalkynyl, substituted or
 30

-399-

unsubstituted heterocyclyl, substituted or unsubstituted cycloalkylalkyl and substituted or unsubstituted heterocyclylalkyl;

R^2 is hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or
 5 unsubstituted aryl;

R^3 and R^4 are selected from (i) and (ii) as follows:

(i) R^3 is substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or
 10 unsubstituted alkylaminocarbonyl or $C(J)OR^{30}$; and R^4 is hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, halide, pseudohalide, hydroxycarbonyl, $C(J)R^{30}$, $C(J)NR^{31}R^{32}$, $CH_2NR^{31}R^{32}$, CH_2OR^{31} , $CR^{30}=CR^{31}R^{32}$, NO_2 or $NR^{31}R^{32}$; and

15 (ii) R^3 and R^4 , together with the atoms to which they are attached, form a substituted or unsubstituted heterocyclic ring;

R^5 is substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted aryl, substituted
 20 or unsubstituted heteroaryl, substituted or unsubstituted aralkyl, substituted or unsubstituted aralkenyl, substituted or unsubstituted aralkynyl, substituted or unsubstituted heteroaralkyl, substituted or unsubstituted heteroaralkenyl, substituted or unsubstituted heteroaralkynyl, $-N=CR^6R^7$ or $-NR^9R^{10}$;

25 R^6 and R^7 are each independently hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted

-400-

aralkyl, or substituted or unsubstituted heteroaralkyl; or together form substituted or unsubstituted alkylene, substituted or unsubstituted alkenylene, substituted or unsubstituted alkynylene, or $-(CH_2)_xX(CH_2)_y-$ where x and y are each independently 1, 2 or 3, and X is O, S or NR^8 ;

5 R^8 is substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted alkylcarbonyl, substituted or unsubstituted arylcarbonyl, or substituted or unsubstituted heteroarylcarbonyl;

R^9 and R^{10} are each independently hydrogen, substituted or
10 unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted aralkyl, or substituted or unsubstituted heteroaralkyl;

R^{30} is hydrogen, substituted or unsubstituted alkyl, substituted or
15 unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted cycloalkylalkyl, substituted or unsubstituted heterocyclalkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted aralkyl, or
20 substituted or unsubstituted heteroaralkyl;

R^{31} and R^{32} are each independently hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted
25 cycloalkylalkyl, substituted or unsubstituted heterocyclalkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted aralkyl, substituted or unsubstituted heteroaralkyl, or $C(J)R^{35}$; or R^{31} and R^{32} , together with the atoms to which they are attached, form substituted or unsubstituted cycloalkyl ring, a substituted

-401-

or unsubstituted heterocyclic ring or a substituted or unsubstituted heteroaryl ring;

J is O, S or NR^{40} ;

R^{35} is hydrogen, substituted or unsubstituted alkyl, substituted or
 5 unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or
 unsubstituted cycloalkyl, substituted or unsubstituted heterocyclyl,
 substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl,
 substituted or unsubstituted alkoxy, substituted or unsubstituted
 aralkoxy, substituted or unsubstituted alkylamino, substituted or
 10 unsubstituted dialkylamino, substituted or unsubstituted arylalkylamino,
 or substituted or unsubstituted diarylamino;

R^{40} is hydrogen, substituted or unsubstituted alkyl, substituted or
 unsubstituted aryl, or substituted or unsubstituted heteroaryl;

where the alkyl, alkenyl, alkynyl, cycloalkyl, heterocyclyl, alkylene,
 15 alkenylene, alkynylene, aryl, heteroaryl, aralkyl, aralkenyl, aralkynyl,
 heteroaralkyl, heteroaralkenyl and heteroaralkynyl moieties of R^1 , R^2 , R^3 ,
 R^5 , R^6 , R^7 , R^8 , R^9 and R^{10} are unsubstituted or substituted with one or
 more substituents, in one embodiment one to three or four substituents,
 each independently selected from Q^1 , where Q^1 is halo, pseudohalo,
 20 hydroxy, oxo, thia, nitrile, nitro, formyl, mercapto, amino, hydroxyalkyl,
 hydroxyalkylaryloxy, hydroxyaryl, hydroxyalkylaryl, hydroxycarbonyl,
 hydroxycarbonylalkyl, alkyl, haloalkyl, polyhaloalkyl, aminoalkyl,
 diaminoalkyl, alkenyl containing 1 to 2 double bonds, alkynyl containing
 1 to 2 triple bonds, cycloalkyl, cycloalkylalkyl, heterocyclyl,
 25 heterocyclylalkyl, aryl, diaryl, hydroxyaryl, alkylaryl, heteroaryl, aralkyl,
 aralkenyl, aralkynyl, alkylaralkyl, heteroarylalkyl, trialkylsilyl,
 dialkylarylsilyl, alkyl diarylsilyl, triarylsilyl, alkylidene, arylalkylidene,
 alkylcarbonyl, alkylarylcarbonyl, arylcarbonyl, heterocyclylcarbonyl,
 heteroarylcarbonyl, alkoxycarbonyl, alkoxycarbonylalkyl,

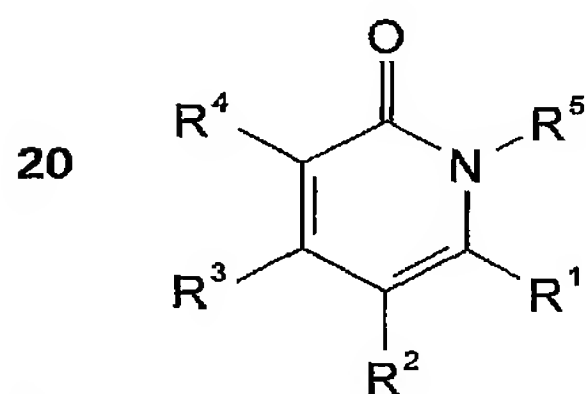
-402-

- alkoxycarbonylaryloxy, aryloxycarbonyl, aryloxycarbonylalkyl, heterocyclylcarbonylalkylaryl, aralkoxycarbonyl, aralkoxycarbonylalkyl, arylcarbonylalkyl, aminocarbonyl, alkylaminocarbonyl, dialkylaminocarbonyl, arylaminocarbonyl, diarylaminocarbonyl,
- 5 arylalkylaminocarbonyl, alkoxy, aryloxy, haloalkoxy, alkoxyaryloxy, alkylaryloxy, diaryloxy, alkylaryloxyalkyl, alkylidiaryloxy, perfluoroalkoxy, alkenyloxy, alkynyloxy, aryloxyalkoxy, aralkoxyaryloxy, alkylarylcycloalkyloxy, heterocycloxy, alkoxyalkyl, alkoxyalkoxyalkyl, alkylheteroaryloxy, alkylcycloalkoxy, cycloalkyloxy, heterocyclyloxy,
- 10 aralkoxy, haloaryloxy, heteroaryloxy, alkylheteroaryloxy, alkoxycarbonylheterocycloxy, alkylcarbonylaryloxy, alkylcarbonyloxy, arylcarbonyloxy, aralkylcarbonyloxy, alkoxycarbonyloxy, aryloxycarbonyloxy, alkoxyaryloxy, aralkoxycarbonyloxy, ureido, alkylureido, arylureido, amino, aminoalkyl, alkylaminoalkyl, dialkylaminoalkyl, aryl-
- 15 aminoalkyl, diarylaminoalkyl, alkylarylaminoalkyl, alkylamino, dialkylamino, haloalkylamino, haloalkylarylamino, arylamino, diarylamino, alkylarylamino, aralkylamino, alkylcarbonylamino, aralkylcarbonylamino, haloalkylcarbonylamino, alkoxycarbonylamino, aralkoxycarbonylamino, arylcarbonylamino, arylcarbonylaminoalkyl, aryloxycarbonylaminoalkyl,
- 20 aryloxyarylcarbonylamino, aryloxycarbonylamino, alkylenedioxyalkyl, dialkylalkylenedioxyalkyl, alkylsulfonylamino, arylsulfonylamino, azido, dialkylphosphonyl, alkylarylphosphonyl, diarylphosphonyl, alkylthio, arylthio, perfluoroalkylthio, hydroxycarbonylalkylthio, thiocyano, isothiocyano, alkylsulfinyl, alkylsulfonyl, arylsulfinyl, arylsulfonyl,
- 25 aminosulfonyl, alkylaminosulfonyl, dialkylaminosulfonyl, arylaminosulfonyl, diarylaminosulfonyl or alkylarylaminosulfonyl; or two Q¹ groups, which substitute atoms in a 1,2 or 1,3 arrangement, together form alkylenedioxy (*i.e.*, -O-(CH₂)_z-O-), thioalkylenoxy (*i.e.*, -S-(CH₂)_z-O-) or alkylenedithioxy (*i.e.*, -S-(CH₂)_z-S-) where z is 1 or 2; and

-403-

each Q¹ is independently unsubstituted or substituted with one or more substituents, in one embodiment one to three or four substituents, each independently selected from Q², where Q² is halo, pseudohalo, hydroxy, oxo, thia, nitrile, nitro, formyl, mercapto, amino, hydroxyalkyl, hydroxyaryl, hydroxycarbonyl, alkyl, haloalkyl, polyhaloalkyl, aminoalkyl, diaminoalkyl, alkenyl containing 1 to 2 double bonds, alkynyl containing 1 to 2 triple bonds, cycloalkyl, heterocyclyl, aryl, heteroaryl, aralkyl, aralkenyl, aralkynyl, alkoxycarbonyl, aryloxycarbonyl, aralkoxycarbonyl, arylcarbonylalkyl, aminocarbonyl, alkoxy, aryloxy, aralkoxy, alkylenedioxy, amino, aminoalkyl, dialkylamino, arylamino, diarylamino, alkylamino, dialkylamino, haloalkylamino, arylamino, diarylamino, alkyl-aryl-amino, aralkylamino, alkoxycarbonylamino, arylcarbonylamino, alkylthio or arylthio.

131. A method of modulating nuclear receptor activity, comprising contacting the nuclear receptor with a compound of formula I:



or a pharmaceutically acceptable derivative thereof, wherein:

R¹ is selected from substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted aralkyl, substituted or unsubstituted heteroaralkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted

-404-

cycloalkenyl, substituted or unsubstituted cycloalkynyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted cycloalkylalkyl and substituted or unsubstituted heterocyclalkyl;

R^2 is hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted aryl;

R^3 and R^4 are selected from (i) and (ii) as follows:

(i) R^3 is substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted alkylaminocarbonyl or $C(J)OR^{30}$; and R^4 is hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, halide, pseudohalide, hydroxycarbonyl, $C(J)R^{30}$, $C(J)NR^{31}R^{32}$, $CH_2NR^{31}R^{32}$, CH_2OR^{31} , $CR^{30}=CR^{31}R^{32}$, NO_2 or $NR^{31}R^{32}$; and

(ii) R^3 and R^4 , together with the atoms to which they are attached, form a substituted or unsubstituted heterocyclic ring;

R^5 is substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted aralkyl, substituted or unsubstituted aralkenyl, substituted or unsubstituted aralkynyl, substituted or unsubstituted heteroaralkyl, substituted or unsubstituted heteroaralkenyl, substituted or unsubstituted heteroaralkynyl, $-N=CR^6R^7$ or $-NR^9R^{10}$;

R^6 and R^7 are each independently hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted aryl,

-405-

- substituted or unsubstituted heteroaryl, substituted or unsubstituted aralkyl, or substituted or unsubstituted heteroaralkyl; or together form substituted or unsubstituted alkylene, substituted or unsubstituted alkenylene, substituted or unsubstituted alkynylene, or $-(CH_2)_xX(CH_2)_y-$ where x and y are each independently 1, 2 or 3, and X is O, S or NR^8 ;
- 5 R^8 is substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted alkylcarbonyl, substituted or unsubstituted arylcarbonyl, or substituted or unsubstituted heteroarylcarbonyl;
- 10 R^9 and R^{10} are each independently hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted aralkyl, or substituted or unsubstituted heteroaralkyl;
- 15 R^{30} is hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted cycloalkylalkyl, substituted or unsubstituted heterocyclalkyl, substituted or unsubstituted aryl, substituted or
- 20 unsubstituted heteroaryl, substituted or unsubstituted aralkyl, or substituted or unsubstituted heteroaralkyl;
- R^{31} and R^{32} are each independently hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted cycloalkyl, substituted
- 25 or unsubstituted heterocyclyl, substituted or unsubstituted cycloalkylalkyl, substituted or unsubstituted heterocyclalkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted aralkyl, substituted or unsubstituted heteroaralkyl, or $C(J)R^{35}$; or R^{31} and R^{32} , together with the atoms to which they are

-406-

attached, form substituted or unsubstituted cycloalkyl ring, a substituted or unsubstituted heterocyclic ring or a substituted or unsubstituted heteroaryl ring;

J is O, S or NR⁴⁰;

- 5 R³⁵ is hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted alkoxy, substituted or unsubstituted
- 10 aralkoxy, substituted or unsubstituted alkylamino, substituted or unsubstituted dialkylamino, substituted or unsubstituted arylalkylamino, or substituted or unsubstituted diarylamino;

R⁴⁰ is hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl;

- 15 where the alkyl, alkenyl, alkynyl, cycloalkyl, heterocyclyl, alkylene, alkenylene, alkynylene, aryl, heteroaryl, aralkyl, aralkenyl, aralkynyl, heteroaralkyl, heteroaralkenyl and heteroaralkynyl moieties of R¹, R², R³, R⁵, R⁶, R⁷, R⁸, R⁹ and R¹⁰ are unsubstituted or substituted with one or more substituents, in one embodiment one to three or four substituents,
- 20 each independently selected from Q¹, where Q¹ is halo, pseudohalo, hydroxy, oxo, thia, nitrile, nitro, formyl, mercapto, amino, hydroxyalkyl, hydroxyalkylaryloxy, hydroxyaryl, hydroxyalkylaryl, hydroxycarbonyl, hydroxycarbonylalkyl, alkyl, haloalkyl, polyhaloalkyl, aminoalkyl, diaminoalkyl, alkenyl containing 1 to 2 double bonds, alkynyl containing
- 25 1 to 2 triple bonds, cycloalkyl, cycloalkylalkyl, heterocyclyl, heterocyclylalkyl, aryl, diaryl, hydroxyaryl, alkylaryl, heteroaryl, aralkyl, aralkenyl, aralkynyl, alkylaralkyl, heteroarylalkyl, trialkylsilyl, dialkylarylsilyl, alkyl diarylsilyl, triarylsilyl, alkylidene, arylalkylidene, alkylcarbonyl, alkylarylcarbonyl, arylcarbonyl, heterocyclylcarbonyl,

-407-

- heteroarylcarbonyl, alkoxycarbonyl, alkoxycarbonylalkyl, alkoxycarbonylaryloxy, aryloxycarbonyl, aryloxycarbonylalkyl, heterocyclylcarbonylalkylaryl, aralkoxycarbonyl, aralkoxycarbonylalkyl, arylcarbonylalkyl, aminocarbonyl, alkylaminocarbonyl,
- 5 dialkylaminocarbonyl, arylaminocarbonyl, diarylaminocarbonyl, arylalkylaminocarbonyl, alkoxy, aryloxy, haloalkoxy, alkoxyaryloxy, alkylaryloxy, diaryloxy, alkylaryloxyalkyl, alkyl diaryloxy, perfluoroalkoxy, alkenyloxy, alkynyloxy, aryloxyalkoxy, aralkoxyaryloxy, alkylarylcyloalkyloxy, heterocycloxy, alkoxyalkyl, alkoxyalkoxyalkyl,
- 10 alkylheteroaryloxy, alkylcyloalkoxy, cycloalkyloxy, heterocyclyloxy, aralkoxy, haloaryloxy, heteroaryloxy, alkylheteroaryloxy, alkoxycarbonylheterocycloxy, alkylcarbonylaryloxy, alkylcarbonyloxy, arylcarbonyloxy, aralkylcarbonyloxy, alkoxycarbonyloxy, aryloxycarbonyloxy, alkoxyaryloxy, aralkoxycarbonyloxy, ureido, alkylureido, aryl-
- 15 ureido, amino, aminoalkyl, alkylaminoalkyl, dialkylaminoalkyl, arylaminoalkyl, diarylaminoalkyl, alkylarylaminominoalkyl, alkylamino, dialkylamino, haloalkylamino, haloalkylarylaminomino, arylamino, diarylamino, alkylarylaminomino, aralkylamino, alkylcarbonylamino, aralkylcarbonylamino, haloalkylcarbonylamino, alkoxycarbonylamino, aralkoxycarbonylamino,
- 20 arylcarbonylamino, arylcarbonylaminoalkyl, aryloxycarbonylaminoalkyl, aryloxyarylcarbonylamino, aryloxycarbonylamino, alkylenedioxyalkyl, dialkylalkylenedioxyalkyl, alkylsulfonylamino, arylsulfonylamino, azido, dialkylphosphonyl, alkylarylphosphonyl, diarylphosphonyl, alkylthio, arylthio, perfluoroalkylthio, hydroxycarbonylalkylthio, thiocyano,
- 25 isothiocyano, alkylsulfinyl, alkylsulfonyl, arylsulfinyl, arylsulfonyl, aminosulfonyl, alkylaminosulfonyl, dialkylaminosulfonyl, arylaminosulfonyl, diarylamino sulfonyl or alkylarylaminosulfonyl; or two Q¹ groups, which substitute atoms in a 1,2 or 1,3 arrangement, together

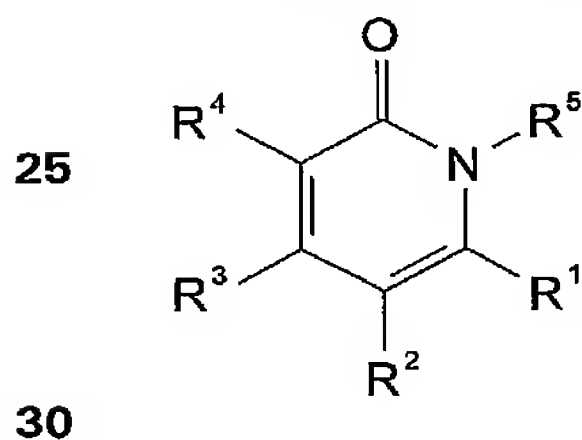
-408-

form alkylenedioxy (*i.e.*, -O-(CH₂)_z-O-), thioalkylenoxy (*i.e.*,
 -S-(CH₂)_z-O-) or alkylenedithioxy (*i.e.*, -S-(CH₂)_z-S-) where z is 1 or 2; and
 each Q¹ is independently unsubstituted or substituted with one or
 more substituents, in one embodiment one to three or four substituents,
 5 each independently selected from Q², where Q² is halo, pseudohalo,
 hydroxy, oxo, thia, nitrile, nitro, formyl, mercapto, amino, hydroxyalkyl,
 hydroxyaryl, hydroxycarbonyl, alkyl, haloalkyl, polyhaloalkyl, aminoalkyl,
 diaminoalkyl, alkenyl containing 1 to 2 double bonds, alkynyl containing
 1 to 2 triple bonds, cycloalkyl, heterocyclyl, aryl, heteroaryl, aralkyl,
 10 aralkenyl, aralkynyl, alkoxycarbonyl, aryloxycarbonyl, aralkoxycarbonyl,
 arylcarbonylalkyl, aminocarbonyl, alkoxy, aryloxy, aralkoxy,
 alkylenedioxy, amino, aminoalkyl, dialkylamino, arylamino, diarylamino,
 alkylamino, dialkylamino, haloalkylamino, arylamino, diarylamino, alkyl-
 arylamino, aralkylamino, alkoxycarbonylamino, arylcarbonylamino,
 15 alkylthio or arylthio.

132. The method of claim 131, wherein the nuclear receptor is an
 orphan nuclear receptor.

133. The method of claim 131, wherein the nuclear receptor is
 liver X receptor (LXR α or LXR β).

20 134. A method of modulating cholesterol metabolism, comprising
 administering an effective amount of a compound of formula I:



or a pharmaceutically acceptable derivative thereof, wherein:

-409-

R¹ is selected from substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted aralkyl, substituted or unsubstituted heteroaralkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted cycloalkenyl, substituted or unsubstituted cycloalkynyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted cycloalkylalkyl and substituted or unsubstituted heterocyclylalkyl;

R² is hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted aryl;

R³ and R⁴ are selected from (i) and (ii) as follows:

(i) R³ is substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted alkylaminocarbonyl or C(J)OR³⁰; and R⁴ is hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, halide, pseudohalide, hydroxycarbonyl, C(J)R³⁰, C(J)NR³¹R³², CH₂NR³¹R³², CH₂OR³¹, CR³⁰=CR³¹R³², NO₂ or NR³¹R³²; and

(ii) R³ and R⁴, together with the atoms to which they are attached, form a substituted or unsubstituted heterocyclic ring;

R⁵ is substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted aralkyl, substituted or unsubstituted aralkenyl, substituted or unsubstituted aralkynyl, substituted or unsubstituted heteroaralkyl, substituted or

-410-

unsubstituted heteroaralkenyl, substituted or unsubstituted heteroaralkynyl, $-N=CR^6R^7$ or $-NR^9R^{10}$;

R^6 and R^7 are each independently hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted aralkyl, or substituted or unsubstituted heteroaralkyl; or together form substituted or unsubstituted alkylene, substituted or unsubstituted alkenylene, substituted or unsubstituted alkynylene, or $-(CH_2)_xX(CH_2)_y-$ where x and y are each independently 1, 2 or 3, and X is O, S or NR^8 ;

R^8 is substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted alkylcarbonyl, substituted or unsubstituted arylcarbonyl, or substituted or unsubstituted heteroarylcarbonyl;

R^9 and R^{10} are each independently hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted aralkyl, or substituted or unsubstituted heteroaralkyl;

R^{30} is hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted cycloalkylalkyl, substituted or unsubstituted heterocyclylalkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted aralkyl, or substituted or unsubstituted heteroaralkyl;

R^{31} and R^{32} are each independently hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or

-411-

- unsubstituted alkynyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted cycloalkylalkyl, substituted or unsubstituted heterocyclalkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted aralkyl, substituted or unsubstituted heteroaralkyl, or C(J)R³⁵; or R³¹ and R³², together with the atoms to which they are attached, form substituted or unsubstituted cycloalkyl ring, a substituted or unsubstituted heterocyclic ring or a substituted or unsubstituted heteroaryl ring;
- 10 J is O, S or NR⁴⁰;
- R³⁵ is hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted alkoxy, substituted or unsubstituted aralkoxy, substituted or unsubstituted alkylamino, substituted or unsubstituted dialkylamino, substituted or unsubstituted arylalkylamino, or substituted or unsubstituted diarylamino;
- 15 R⁴⁰ is hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl;
- 20 where the alkyl, alkenyl, alkynyl, cycloalkyl, heterocyclyl, alkylene, alkenylene, alkynylene, aryl, heteroaryl, aralkyl, aralkenyl, aralkynyl, heteroaralkyl, heteroaralkenyl and heteroaralkynyl moieties of R¹, R², R³, R⁵, R⁶, R⁷, R⁸, R⁹ and R¹⁰ are unsubstituted or substituted with one or
- 25 more substituents, in one embodiment one to three or four substituents, each independently selected from Q¹, where Q¹ is halo, pseudohalo, hydroxy, oxo, thia, nitrile, nitro, formyl, mercapto, amino, hydroxyalkyl, hydroxyalkylaryloxy, hydroxyaryl, hydroxyalkylaryl, hydroxycarbonyl, hydroxycarbonylalkyl, alkyl, haloalkyl, polyhaloalkyl, aminoalkyl,

-412-

- diaminoalkyl, alkenyl containing 1 to 2 double bonds, alkynyl containing 1 to 2 triple bonds, cycloalkyl, cycloalkylalkyl, heterocyclyl, heterocyclylalkyl, aryl, diaryl, hydroxyaryl, alkylaryl, heteroaryl, aralkyl, aralkenyl, aralkynyl, alkylaralkyl, heteroarylalkyl, trialkylsilyl,
- 5 dialkylarylsilyl, alkyl diarylsilyl, triarylsilyl, alkylidene, arylalkylidene, alkylcarbonyl, alkylarylcarbonyl, arylcarbonyl, heterocyclylcarbonyl, heteroarylcarbonyl, alkoxycarbonyl, alkoxycarbonylalkyl, alkoxycarbonylaryloxy, aryloxy carbonyl, aryloxy carbonylalkyl, heterocyclylcarbonylalkylaryl, aralkoxycarbonyl, aralkoxycarbonylalkyl,
- 10 arylcarbonylalkyl, aminocarbonyl, alkylaminocarbonyl, dialkylaminocarbonyl, arylaminocarbonyl, diarylaminocarbonyl, arylalkylaminocarbonyl, alkoxy, aryloxy, haloalkoxy, alkoxyaryloxy, alkylaryloxy, diaryloxy, alkylaryloxyalkyl, alkyl diaryloxy, perfluoroalkoxy, alkenyloxy, alkynyloxy, aryloxyalkoxy, aralkoxyaryloxy,
- 15 alkylaryl cycloalkyloxy, heterocycloxy, alkoxyalkyl, alkoxyalkoxyalkyl, alkylheteroaryloxy, alkyl cycloalkoxy, cycloalkyloxy, heterocycliloxy, aralkoxy, haloaryloxy, heteroaryloxy, alkylheteroaryloxy, alkoxycarbonyl heterocycloxy, alkylcarbonylaryloxy, alkylcarbonyloxy, arylcarbonyloxy, aralkylcarbonyloxy, alkoxycarbonyloxy, aryloxy carbonyloxy, alkoxyaryloxy, aralkoxycarbonyloxy, ureido, alkylureido, aryl-
- 20 ureido, amino, aminoalkyl, alkylaminoalkyl, dialkylaminoalkyl, arylaminoalkyl, diarylaminoalkyl, alkylaryl aminoalkyl, alkylamino, dialkylamino, haloalkylamino, haloalkylaryl amino, arylamino, diarylamino, alkylaryl amino, aralkylamino, alkylcarbonylamino, aralkylcarbonylamino,
- 25 haloalkylcarbonylamino, alkoxycarbonylamino, aralkoxycarbonylamino, arylcarbonylamino, arylcarbonylaminoalkyl, aryloxy carbonylaminoalkyl, aryloxyaryl carbonylamino, aryloxy carbonylamino, alkylenedioxyalkyl, dialkylalkylenedioxyalkyl, alkylsulfonylamino, arylsulfonylamino, azido, dialkylphosphonyl, alkylarylphosphonyl, diarylphosphonyl, alkylthio, aryl-

-413-

thio, perfluoroalkylthio, hydroxycarbonylalkylthio, thiocyano, isothiocyano, alkylsulfinyl, alkylsulfonyl, arylsulfinyl, arylsulfonyl, aminosulfonyl, alkylaminosulfonyl, dialkylaminosulfonyl, arylaminosulfonyl, diarylaminosulfonyl or alkylarylaminosulfonyl; or two

5 Q¹ groups, which substitute atoms in a 1,2 or 1,3 arrangement, together form alkylenedioxy (*i.e.*, -O-(CH₂)_z-O-), thioalkylenoxy (*i.e.*, -S-(CH₂)_z-O-) or alkylenedithioxy (*i.e.*, -S-(CH₂)_z-S-) where z is 1 or 2; and each Q¹ is independently unsubstituted or substituted with one or more substituents, in one embodiment one to three or four substituents,

10 each independently selected from Q², where Q² is halo, pseudohalo, hydroxy, oxo, thia, nitrile, nitro, formyl, mercapto, amino, hydroxyalkyl, hydroxyaryl, hydroxycarbonyl, alkyl, haloalkyl, polyhaloalkyl, aminoalkyl, diaminoalkyl, alkenyl containing 1 to 2 double bonds, alkynyl containing 1 to 2 triple bonds, cycloalkyl, heterocyclyl, aryl, heteroaryl, aralkyl,

15 aralkenyl, aralkynyl, alkoxycarbonyl, aryloxycarbonyl, aralkoxycarbonyl, arylcarbonylalkyl, aminocarbonyl, alkoxy, aryloxy, aralkoxy, alkylenedioxy, amino, aminoalkyl, dialkylamino, arylamino, diarylamino, alkylamino, dialkylamino, haloalkylamino, arylamino, diarylamino, alkyl-arylaminosulfonyl, aralkylaminosulfonyl, alkoxycarbonylamino, arylcarbonylamino,

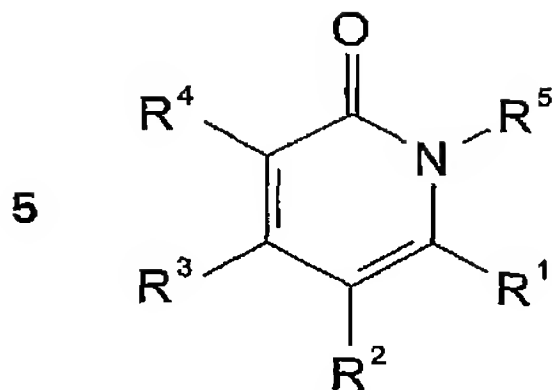
20 alkylthio or arylthio.

135. A method of treating, preventing or ameliorating one or more symptoms of hypocholesterolemia in a subject in need thereof, comprising administering an effective amount of a compound of formula I:

25

30

-414-



or a pharmaceutically acceptable derivative thereof, wherein:

R^1 is selected from substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted aralkyl, substituted or unsubstituted heteroaralkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted cycloalkenyl, substituted or unsubstituted cycloalkynyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted cycloalkylalkyl and substituted or unsubstituted heterocyclylalkyl;

R^2 is hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted aryl;

R^3 and R^4 are selected from (i) and (ii) as follows:

(i) R^3 is substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted alkylaminocarbonyl or $C(J)OR^{30}$; and R^4 is hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, halide, pseudohalide, hydroxycarbonyl, $C(J)R^{30}$, $C(J)NR^{31}R^{32}$, $CH_2NR^{31}R^{32}$, CH_2OR^{31} , $CR^{30}=CR^{31}R^{32}$, NO_2 or $NR^{31}R^{32}$; and

(ii) R^3 and R^4 , together with the atoms to which they are attached, form a substituted or unsubstituted heterocyclic ring;

-415-

R⁵ is substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted aralkyl, substituted or unsubstituted aralkenyl, substituted or unsubstituted aralkynyl, substituted or unsubstituted heteroaralkyl, substituted or unsubstituted heteroaralkenyl, substituted or unsubstituted heteroaralkynyl, -N=CR⁶R⁷ or -NR⁹R¹⁰;

R⁶ and R⁷ are each independently hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted aralkyl, or substituted or unsubstituted heteroaralkyl; or together form substituted or unsubstituted alkylene, substituted or unsubstituted alkenylene, substituted or unsubstituted alkynylene, or -(CH₂)_xX(CH₂)_y- where x and y are each independently 1, 2 or 3, and X is O, S or NR⁸;

R⁸ is substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted alkylcarbonyl, substituted or unsubstituted arylcarbonyl, or substituted or unsubstituted heteroarylcarbonyl;

R⁹ and R¹⁰ are each independently hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted aralkyl, or substituted or unsubstituted heteroaralkyl;

R³⁰ is hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocyclyl,

-416-

substituted or unsubstituted cycloalkylalkyl, substituted or unsubstituted heterocyclalkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted aralkyl, or substituted or unsubstituted heteroaralkyl;

- 5 R^{31} and R^{32} are each independently hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycl, substituted or unsubstituted cycloalkylalkyl, substituted or unsubstituted heterocyclalkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted aralkyl, substituted or unsubstituted heteroaralkyl, or $C(J)R^{35}$; or R^{31} and R^{32} , together with the atoms to which they are attached, form substituted or unsubstituted cycloalkyl ring, a substituted or unsubstituted heterocyclic ring or a substituted or unsubstituted heteroaryl ring;

J is O, S or NR^{40} ;

- R^{35} is hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted alkoxy, substituted or unsubstituted aralkoxy, substituted or unsubstituted alkylamino, substituted or unsubstituted dialkylamino, substituted or unsubstituted arylalkylamino, or substituted or unsubstituted diarylamino;

- 25 R^{40} is hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl;

where the alkyl, alkenyl, alkynyl, cycloalkyl, heterocycl, alkylene, alkenylene, alkynylene, aryl, heteroaryl, aralkyl, aralkenyl, aralkynyl, heteroaralkyl, heteroaralkenyl and heteroaralkynyl moieties of R^1 , R^2 , R^3 ,

-417-

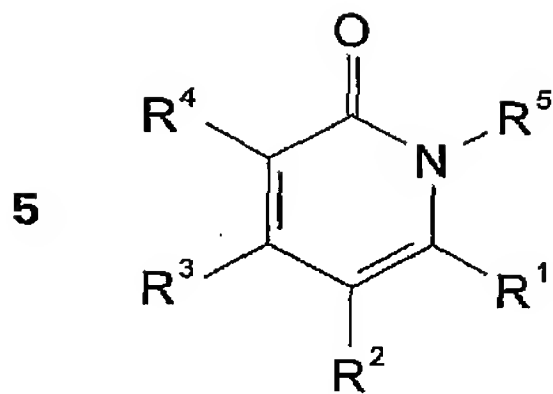
R^5 , R^6 , R^7 , R^8 , R^9 and R^{10} are unsubstituted or substituted with one or more substituents, in one embodiment one to three or four substituents, each independently selected from Q^1 , where Q^1 is halo, pseudohalo, hydroxy, oxo, thia, nitrile, nitro, formyl, mercapto, amino, hydroxyalkyl, hydroxyalkylaryloxy, hydroxyaryl, hydroxyalkylaryl, hydroxycarbonyl, hydroxycarbonylalkyl, alkyl, haloalkyl, polyhaloalkyl, aminoalkyl, diaminoalkyl, alkenyl containing 1 to 2 double bonds, alkynyl containing 1 to 2 triple bonds, cycloalkyl, cycloalkylalkyl, heterocyclyl, heterocyclylalkyl, aryl, diaryl, hydroxyaryl, alkylaryl, heteroaryl, aralkyl, aralkenyl, aralkynyl, alkylaralkyl, heteroarylalkyl, trialkylsilyl, dialkylarylsilyl, alkyl diarylsilyl, triarylsilyl, alkylidene, arylalkylidene, alkylcarbonyl, alkylarylcarbonyl, arylcarbonyl, heterocyclylcarbonyl, heteroarylcarbonyl, alkoxycarbonyl, alkoxycarbonylalkyl, alkoxycarbonylaryloxy, aryloxycarbonyl, aryloxycarbonylalkyl, heterocyclylcarbonylalkylaryl, aralkoxycarbonyl, aralkoxycarbonylalkyl, arylcarbonylalkyl, aminocarbonyl, alkylaminocarbonyl, dialkylaminocarbonyl, arylaminocarbonyl, diarylaminocarbonyl, arylalkylaminocarbonyl, alkoxy, aryloxy, haloalkoxy, alkoxyaryloxy, alkylaryloxy, diaryloxy, alkylaryloxyalkyl, alkyl diaryloxy, perfluoroalkoxy, alkenyloxy, alkynyloxy, aryloxyalkoxy, aralkoxyaryloxy, alkylarylcyloalkoxy, heterocycloxy, alkoxyalkyl, alkoxyalkoxyalkyl, alkylheteroaryloxy, alkylcyloalkoxy, cycloalkoxy, heterocyclioxy, aralkoxy, haloaryloxy, heteroaryloxy, alkylheteroaryloxy, alkoxycarbonylheterocycloxy, alkylcarbonylaryloxy, alkylcarbonyloxy, arylcarbonyloxy, aralkylcarbonyloxy, alkoxycarbonyloxy, aryloxycarbonyloxy, alkoxyaryloxy, aralkoxycarbonyloxy, ureido, alkylureido, arylureido, amino, aminoalkyl, alkylaminoalkyl, dialkylaminoalkyl, arylaminoalkyl, diarylaminoalkyl, alkylarylaminalkyl, alkylamino, dialkylamino, haloalkylamino, haloalkylarylamin, arylamino, diarylamino, alkyl-

-418-

- arylamino, aralkylamino, alkylcarbonylamino, aralkylcarbonylamino, haloalkylcarbonylamino, alkoxycarbonylamino, aralkoxycarbonylamino, arylcarbonylamino, arylcarbonylaminoalkyl, aryloxycarbonylaminoalkyl, aryloxyarylcarbonylamino, aryloxycarbonylamino, alkylenedioxyalkyl, dialkylalkylenedioxyalkyl, alkylsulfonylamino, arylsulfonylamino, azido, dialkylphosphonyl, alkylarylphosphonyl, diarylphosphonyl, alkylthio, arylthio, perfluoroalkylthio, hydroxycarbonylalkylthio, thiocyano, isothiocyano, alkylsulfinyl, alkylsulfonyl, arylsulfinyl, arylsulfonyl, aminosulfonyl, alkylaminosulfonyl, dialkylaminosulfonyl, arylaminosulfonyl, diarylaminosulfonyl or alkylarylaminosulfonyl; or two Q^1 groups, which substitute atoms in a 1,2 or 1,3 arrangement, together form alkylenedioxy (*i.e.*, $-O-(CH_2)_z-O-$), thioalkylenoxy (*i.e.*, $-S-(CH_2)_z-O-$) or alkylenedithioxy (*i.e.*, $-S-(CH_2)_z-S-$) where z is 1 or 2; and each Q^1 is independently unsubstituted or substituted with one or more substituents, in one embodiment one to three or four substituents, each independently selected from Q^2 , where Q^2 is halo, pseudohalo, hydroxy, oxo, thia, nitrile, nitro, formyl, mercapto, amino, hydroxyalkyl, hydroxyaryl, hydroxycarbonyl, alkyl, haloalkyl, polyhaloalkyl, aminoalkyl, diaminoalkyl, alkenyl containing 1 to 2 double bonds, alkynyl containing 1 to 2 triple bonds, cycloalkyl, heterocyclyl, aryl, heteroaryl, aralkyl, aralkenyl, aralkynyl, alkoxycarbonyl, aryloxycarbonyl, aralkoxycarbonyl, arylcarbonylalkyl, aminocarbonyl, alkoxy, aryloxy, aralkoxy, alkylenedioxy, amino, aminoalkyl, dialkylamino, arylamino, diarylamino, alkylamino, dialkylamino, haloalkylamino, arylamino, diarylamino, alkyl-arylamino, aralkylamino, alkoxycarbonylamino, arylcarbonylamino, alkylthio or arylthio.

136. A method of increasing cholesterol efflux from cells of a subject, comprising administering an effective amount of a compound of formula I:

-419-



or a pharmaceutically acceptable derivative thereof, wherein:

R¹ is selected from substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted aralkyl, substituted or unsubstituted heteroaralkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted cycloalkenyl, substituted or unsubstituted cycloalkynyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted cycloalkylalkyl and substituted or unsubstituted heterocyclylalkyl;

R² is hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted aryl;

R³ and R⁴ are selected from (i) and (ii) as follows:

(i) R³ is substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted alkylaminocarbonyl or C(J)OR³⁰; and R⁴ is hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, halide, pseudohalide, hydroxycarbonyl, C(J)R³⁰, C(J)NR³¹R³², CH₂NR³¹R³², CH₂OR³¹, CR³⁰=CR³¹R³², NO₂ or NR³¹R³²; and

(ii) R³ and R⁴, together with the atoms to which they are attached, form a substituted or unsubstituted heterocyclic ring;

-420-

R⁵ is substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted aralkyl, substituted or unsubstituted aralkenyl, substituted or unsubstituted aralkynyl, substituted or unsubstituted heteroaralkyl, substituted or unsubstituted heteroaralkenyl, substituted or unsubstituted heteroaralkynyl, -N=CR⁶R⁷ or -NR⁹R¹⁰;

R⁶ and R⁷ are each independently hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted aralkyl, or substituted or unsubstituted heteroaralkyl; or together form substituted or unsubstituted alkylene, substituted or unsubstituted alkenylene, substituted or unsubstituted alkynylene, or -(CH₂)_xX(CH₂)_y- where x and y are each independently 1, 2 or 3, and X is O, S or NR⁸;

R⁸ is substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted alkylcarbonyl, substituted or unsubstituted arylcarbonyl, or substituted or unsubstituted heteroarylcarbonyl;

R⁹ and R¹⁰ are each independently hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted aralkyl, or substituted or unsubstituted heteroaralkyl;

R³⁰ is hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocyclyl,

-421-

substituted or unsubstituted cycloalkylalkyl, substituted or unsubstituted heterocyclalkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted aralkyl, or substituted or unsubstituted heteroaralkyl;

- 5 R^{31} and R^{32} are each independently hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycl, substituted or unsubstituted cycloalkylalkyl, substituted or unsubstituted heterocyclalkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted aralkyl, substituted or unsubstituted heteroaralkyl, or $C(J)R^{35}$; or R^{31} and R^{32} , together with the atoms to which they are attached, form substituted or unsubstituted cycloalkyl ring, a substituted or unsubstituted heterocyclic ring or a substituted or unsubstituted heteroaryl ring;
- 10
- 15

J is O, S or NR^{40} ;

- R^{35} is hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycl,
- 20 substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted alkoxy, substituted or unsubstituted aralkoxy, substituted or unsubstituted alkylamino, substituted or unsubstituted dialkylamino, substituted or unsubstituted arylalkylamino, or substituted or unsubstituted diarylamino;

- 25 R^{40} is hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl;

where the alkyl, alkenyl, alkynyl, cycloalkyl, heterocycl, alkylene, alkenylene, alkynylene, aryl, heteroaryl, aralkyl, aralkenyl, aralkynyl, heteroaralkyl, heteroaralkenyl and heteroaralkynyl moieties of R^1 , R^2 , R^3 ,

-422-

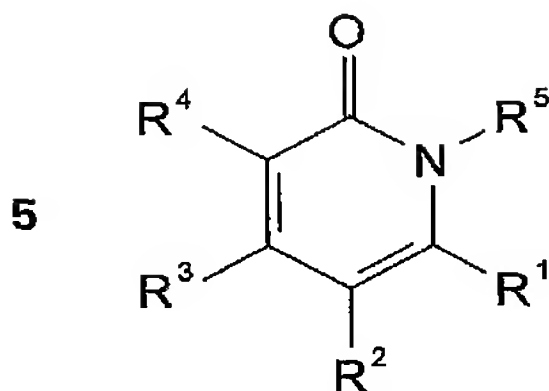
R^5 , R^6 , R^7 , R^8 , R^9 and R^{10} are unsubstituted or substituted with one or more substituents, in one embodiment one to three or four substituents, each independently selected from Q^1 , where Q^1 is halo, pseudohalo, hydroxy, oxo, thia, nitrile, nitro, formyl, mercapto, amino, hydroxyalkyl, hydroxyalkylaryloxy, hydroxyaryl, hydroxyalkylaryl, hydroxycarbonyl, hydroxycarbonylalkyl, alkyl, haloalkyl, polyhaloalkyl, aminoalkyl, diaminoalkyl, alkenyl containing 1 to 2 double bonds, alkynyl containing 1 to 2 triple bonds, cycloalkyl, cycloalkylalkyl, heterocyclyl, heterocyclylalkyl, aryl, diaryl, hydroxyaryl, alkylaryl, heteroaryl, aralkyl, aralkenyl, aralkynyl, alkylaralkyl, heteroarylalkyl, trialkylsilyl, dialkylarylsilyl, alkyl diarylsilyl, triarylsilyl, alkylidene, arylalkylidene, alkylcarbonyl, alkylarylcarbonyl, arylcarbonyl, heterocyclylcarbonyl, heteroarylcarbonyl, alkoxycarbonyl, alkoxycarbonylalkyl, alkoxycarbonylaryloxy, aryloxycarbonyl, aryloxycarbonylalkyl, heterocyclylcarbonylalkylaryl, aralkoxycarbonyl, aralkoxycarbonylalkyl, arylcarbonylalkyl, aminocarbonyl, alkylaminocarbonyl, dialkylaminocarbonyl, arylaminocarbonyl, diarylaminocarbonyl, arylalkylaminocarbonyl, alkoxy, aryloxy, haloalkoxy, alkoxyaryloxy, alkylaryloxy, diaryloxy, alkylaryloxyalkyl, alkyl diaryloxy, perfluoroalkoxy, alkenyloxy, alkynyloxy, aryloxyalkoxy, aralkoxyaryloxy, alkylaryl cycloalkyloxy, heterocycloxy, alkoxyalkyl, alkoxyalkoxyalkyl, alkylheteroaryloxy, alkylcycloalkoxy, cycloalkyloxy, heterocycliloxy, aralkoxy, haloaryloxy, heteroaryloxy, alkylheteroaryloxy, alkoxycarbonylheterocycloxy, alkylcarbonylaryloxy, alkylcarbonyloxy, arylcarbonyloxy, aralkylcarbonyloxy, alkoxycarbonyloxy, aryloxy carbonyloxy, alkoxyaryloxy, aralkoxycarbonyloxy, ureido, alkylureido, arylureido, amino, aminoalkyl, alkylaminoalkyl, dialkylaminoalkyl, arylaminoalkyl, diarylaminoalkyl, alkylaryl aminoalkyl, alkylamino, dialkylamino, haloalkylamino, haloalkylaryl amino, arylamino, diarylamino, alkyl-

-423-

- arylamino, aralkylamino, alkylcarbonylamino, aralkylcarbonylamino, haloalkylcarbonylamino, alkoxycarbonylamino, aralkoxycarbonylamino, arylcarbonylamino, arylcarbonylaminoalkyl, aryloxycarbonylaminoalkyl, aryloxyarylcarbonylamino, aryloxycarbonylamino, alkylenedioxyalkyl, dialkylalkylenedioxyalkyl, alkylsulfonylamino, arylsulfonylamino, azido, dialkylphosphonyl, alkylarylphosphonyl, diarylphosphonyl, alkylthio, arylthio, perfluoroalkylthio, hydroxycarbonylalkylthio, thiocyano, isothiocyano, alkylsulfinyl, alkylsulfonyl, arylsulfinyl, arylsulfonyl, aminosulfonyl, alkylaminosulfonyl, dialkylaminosulfonyl, arylaminosulfonyl, diarylaminosulfonyl or alkylarylaminosulfonyl; or two Q¹ groups, which substitute atoms in a 1,2 or 1,3 arrangement, together form alkylenedioxy (*i.e.*, -O-(CH₂)_z-O-), thioalkylenoxy (*i.e.*, -S-(CH₂)_z-O-) or alkylenedithioxy (*i.e.*, -S-(CH₂)_z-S-) where z is 1 or 2; and each Q¹ is independently unsubstituted or substituted with one or more substituents, in one embodiment one to three or four substituents, each independently selected from Q², where Q² is halo, pseudohalo, hydroxy, oxo, thia, nitrile, nitro, formyl, mercapto, amino, hydroxyalkyl, hydroxyaryl, hydroxycarbonyl, alkyl, haloalkyl, polyhaloalkyl, aminoalkyl, diaminoalkyl, alkenyl containing 1 to 2 double bonds, alkynyl containing 1 to 2 triple bonds, cycloalkyl, heterocyclyl, aryl, heteroaryl, aralkyl, aralkenyl, aralkynyl, alkoxycarbonyl, aryloxycarbonyl, aralkoxycarbonyl, arylcarbonylalkyl, aminocarbonyl, alkoxy, aryloxy, aralkoxy, alkylenedioxy, amino, aminoalkyl, dialkylamino, arylamino, diarylamino, alkylamino, dialkylamino, haloalkylamino, arylamino, diarylamino, alkyl-arylamino, aralkylamino, alkoxycarbonylamino, arylcarbonylamino, alkylthio or arylthio.

137. A method of increasing the expression of ATP-Binding Cassette (ABC1) in the cells of a subject, comprising administering an effective amount of a compound of formula I:

-424-



or a pharmaceutically acceptable derivative thereof, wherein:

R^1 is selected from substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted aralkyl, substituted or unsubstituted heteroaralkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted cycloalkenyl, substituted or unsubstituted cycloalkynyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted cycloalkylalkyl and substituted or unsubstituted heterocyclylalkyl;

R^2 is hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted aryl;

R^3 and R^4 are selected from (i), (ii), (iii) and (iv) as follows:

(i) R^3 is substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted alkylaminocarbonyl or $C(J)OR^{30}$; and R^4 is hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, halide, pseudohalide, hydroxycarbonyl, $C(J)R^{30}$, $C(J)NR^{31}R^{32}$, $CH_2NR^{31}R^{32}$, CH_2OR^{31} , $CR^{30}=CR^{31}R^{32}$, NO_2 or $NR^{31}R^{32}$; and

-425-

(ii) R^3 and R^4 , together with the atoms to which they are attached, form a substituted or unsubstituted heterocyclic ring, or a substituted or unsubstituted heteroaryl ring;

R^5 is substituted or unsubstituted alkyl, substituted or
5 unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or
unsubstituted heterocyclyl, substituted or unsubstituted aryl, substituted
or unsubstituted heteroaryl, substituted or unsubstituted aralkyl,
substituted or unsubstituted aralkenyl, substituted or unsubstituted
aralkynyl, substituted or unsubstituted heteroaralkyl, substituted or
10 unsubstituted heteroaralkenyl, substituted or unsubstituted
heteroaralkynyl, $-N=CR^6R^7$ or $-NR^9R^{10}$;

R^6 and R^7 are each independently hydrogen, substituted or
unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or
unsubstituted alkynyl, substituted or unsubstituted cycloalkyl, substituted
15 or unsubstituted heterocyclyl, substituted or unsubstituted aryl,
substituted or unsubstituted heteroaryl, substituted or unsubstituted
aralkyl, or substituted or unsubstituted heteroaralkyl; or together form
substituted or unsubstituted alkylene, substituted or unsubstituted
alkenylene, substituted or unsubstituted alkynylene, or $-(CH_2)_xX(CH_2)_y-$
20 where x and y are each independently 1, 2 or 3, and X is O, S or NR^8 ;

R^8 is substituted or unsubstituted alkyl, substituted or
unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or
unsubstituted alkylcarbonyl, substituted or unsubstituted arylcarbonyl, or
substituted or unsubstituted heteroarylcarbonyl;

25 R^9 and R^{10} are each independently hydrogen, substituted or
unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or
unsubstituted alkynyl, substituted or unsubstituted aryl, substituted or
unsubstituted heteroaryl, substituted or unsubstituted aralkyl, or
substituted or unsubstituted heteroaralkyl;

-426-

R^{30} is hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted cycloalkylalkyl, substituted or unsubstituted heterocyclylalkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted aralkyl, or substituted or unsubstituted heteroaralkyl;

R^{31} and R^{32} are each independently hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted cycloalkylalkyl, substituted or unsubstituted heterocyclylalkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted aralkyl, substituted or unsubstituted heteroaralkyl, or $C(J)R^{35}$; or R^{31} and R^{32} , together with the atoms to which they are attached, form substituted or unsubstituted cycloalkyl ring, a substituted or unsubstituted heterocyclic ring or a substituted or unsubstituted heteroaryl ring;

J is O, S or NR^{40} ;

R^{35} is hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted alkoxy, substituted or unsubstituted aralkoxy, substituted or unsubstituted alkylamino, substituted or unsubstituted dialkylamino, substituted or unsubstituted arylalkylamino, or substituted or unsubstituted diarylamino;

R^{40} is hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl;

-427-

where the alkyl, alkenyl, alkynyl, cycloalkyl, heterocyclyl, alkylene, alkenylene, alkynylene, aryl, heteroaryl, aralkyl, aralkenyl, aralkynyl, heteroaralkyl, heteroaralkenyl and heteroaralkynyl moieties of R¹, R², R³, R⁵, R⁶, R⁷, R⁸, R⁹ and R¹⁰ are unsubstituted or substituted with one or

5 more substituents, in one embodiment one to three or four substituents, each independently selected from Q¹, where Q¹ is halo, pseudohalo, hydroxy, oxo, thia, nitrile, nitro, formyl, mercapto, amino, hydroxyalkyl, hydroxyalkylaryloxy, hydroxyaryl, hydroxyalkylaryl, hydroxycarbonyl, hydroxycarbonylalkyl, alkyl, haloalkyl, polyhaloalkyl, aminoalkyl,

10 diaminoalkyl, alkenyl containing 1 to 2 double bonds, alkynyl containing 1 to 2 triple bonds, cycloalkyl, cycloalkylalkyl, heterocyclyl, heterocyclylalkyl, aryl, diaryl, hydroxyaryl, alkylaryl, heteroaryl, aralkyl, aralkenyl, aralkynyl, alkylaralkyl, heteroarylalkyl, trialkylsilyl, dialkylarylsilyl, alkyl diarylsilyl, triarylsilyl, alkylidene, arylalkylidene,

15 alkylcarbonyl, alkylarylcarbonyl, arylcarbonyl, heterocyclylcarbonyl, heteroarylcarbonyl, alkoxycarbonyl, alkoxycarbonylalkyl, alkoxycarbonylaryloxy, aryloxycarbonyl, aryloxycarbonylalkyl, heterocyclylcarbonylalkylaryl, aralkoxycarbonyl, aralkoxycarbonylalkyl, arylcarbonylalkyl, aminocarbonyl, alkylaminocarbonyl,

20 dialkylaminocarbonyl, arylaminocarbonyl, diarylaminocarbonyl, arylalkylaminocarbonyl, alkoxy, aryloxy, haloalkoxy, alkoxyaryloxy, alkylaryloxy, diaryloxy, alkylaryloxyalkyl, alkyl diaryloxy, perfluoroalkoxy, alkenyloxy, alkynyloxy, aryloxyalkoxy, aralkoxyaryloxy, alkylarylcycloalkyloxy, heterocycloxy, alkoxyalkyl, alkoxyalkoxyalkyl,

25 alkylheteroaryloxy, alkylcycloalkoxy, cycloalkyloxy, heterocycliloxy, aralkoxy, haloaryloxy, heteroaryloxy, alkylheteroaryloxy, alkoxycarbonylheterocycloxy, alkylcarbonylaryloxy, alkylcarbonyloxy, arylcarbonyloxy, aralkylcarbonyloxy, alkoxycarbonyloxy, aryloxycarbonyloxy, alkoxyaryloxy, aralkoxycarbonyloxy, ureido, alkylureido, aryl-

-428-

ureido, amino, aminoalkyl, alkylaminoalkyl, dialkylaminoalkyl, aryl-aminoalkyl, diarylaminoalkyl, alkylarylaminoalkyl, alkylamino, dialkyl-amino, haloalkylamino, haloalkylarylamino, arylamino, diarylamino, alkyl-arylamino, aralkylamino, alkylcarbonylamino, aralkylcarbonylamino,

5 haloalkylcarbonylamino, alkoxycarbonylamino, aralkoxycarbonylamino, arylcarbonylamino, arylcarbonylaminoalkyl, aryloxycarbonylaminoalkyl, aryloxyarylcabonylamino, aryloxycarbonylamino, alkylenedioxyalkyl, dialkylalkylenedioxyalkyl, alkylsulfonylamino, arylsulfonylamino, azido, dialkylphosphonyl, alkylarylphosphonyl, diarylphosphonyl, alkylthio, aryl-

10 thio, perfluoroalkylthio, hydroxycarbonylalkylthio, thiocyano, isothiocyano, alkylsulfinyl, alkylsulfonyl, arylsulfinyl, arylsulfonyl, aminosulfonyl, alkylaminosulfonyl, dialkylaminosulfonyl, arylaminosulfonyl, diarylaminosulfonyl or alkylarylaminosulfonyl; or two Q^1 groups, which substitute atoms in a 1,2 or 1,3 arrangement, together

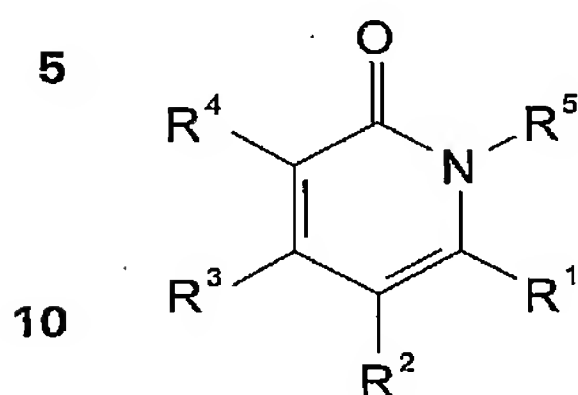
15 form alkylenedioxy (*i.e.*, $-O-(CH_2)_z-O-$), thioalkylenoxy (*i.e.*, $-S-(CH_2)_z-O-$) or alkylenedithioxy (*i.e.*, $-S-(CH_2)_z-S-$) where z is 1 or 2; and each Q^1 is independently unsubstituted or substituted with one or more substituents, in one embodiment one to three or four substituents, each independently selected from Q^2 , where Q^2 is halo, pseudohalo,

20 hydroxy, oxo, thia, nitrile, nitro, formyl, mercapto, amino, hydroxyalkyl, hydroxyaryl, hydroxycarbonyl, alkyl, haloalkyl, polyhaloalkyl, aminoalkyl, diaminoalkyl, alkenyl containing 1 to 2 double bonds, alkynyl containing 1 to 2 triple bonds, cycloalkyl, heterocyclyl, aryl, heteroaryl, aralkyl, aralkenyl, aralkynyl, alkoxycarbonyl, aryloxycarbonyl, aralkoxycarbonyl,

25 arylcarbonylalkyl, aminocarbonyl, alkoxy, aryloxy, aralkoxy, alkylenedioxy, amino, aminoalkyl, dialkylamino, arylamino, diarylamino, alkylamino, dialkylamino, haloalkylamino, arylamino, diarylamino, alkyl-arylamino, aralkylamino, alkoxycarbonylamino, arylcarbonylamino, alkylthio or arylthio.

-429-

138. An *in vitro* method for altering nuclear receptor activity, comprising contacting the nuclear receptor with a compound of formula I:



15 or a pharmaceutically acceptable derivative thereof, wherein:

R¹ is selected from substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted aralkyl, substituted or unsubstituted heteroaralkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted cycloalkenyl, substituted or unsubstituted cycloalkynyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted cycloalkylalkyl and substituted or unsubstituted heterocyclylalkyl;

20

R² is hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted aryl;

25

R³ and R⁴ are selected from (i) and (ii) as follows:

(i) R³ is substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted alkylaminocarbonyl or C(J)OR³⁰; and R⁴ is hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, halide, pseudohalide,

30

-430-

hydroxycarbonyl, $C(J)R^{30}$, $C(J)NR^{31}R^{32}$, $CH_2NR^{31}R^{32}$, CH_2OR^{31} , $CR^{30} = CR^{31}R^{32}$, NO_2 or $NR^{31}R^{32}$; and

(ii) R^3 and R^4 , together with the atoms to which they are attached, form a substituted or unsubstituted heterocyclic ring;

5 R^5 is substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted aralkyl, substituted or unsubstituted aralkenyl, substituted or unsubstituted
10 aralkynyl, substituted or unsubstituted heteroaralkyl, substituted or unsubstituted heteroaralkenyl, substituted or unsubstituted heteroaralkynyl, $-N = CR^6R^7$ or $-NR^9R^{10}$;

R^6 and R^7 are each independently hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or
15 unsubstituted alkynyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted aralkyl, or substituted or unsubstituted heteroaralkyl; or together form substituted or unsubstituted alkylene, substituted or unsubstituted
20 alkenylene, substituted or unsubstituted alkynylene, or $-(CH_2)_xX(CH_2)_y-$ where x and y are each independently 1, 2 or 3, and X is O, S or NR^8 ;

R^8 is substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted alkylcarbonyl, substituted or unsubstituted arylcarbonyl, or
25 substituted or unsubstituted heteroarylcarbonyl;

R^9 and R^{10} are each independently hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted aryl, substituted or

-431-

unsubstituted heteroaryl, substituted or unsubstituted aralkyl, or substituted or unsubstituted heteroaralkyl;

R^{30} is hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or
5 unsubstituted cycloalkyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted cycloalkylalkyl, substituted or unsubstituted heterocyclalkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted aralkyl, or substituted or unsubstituted heteroaralkyl;

10 R^{31} and R^{32} are each independently hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted cycloalkylalkyl, substituted or unsubstituted heterocyclalkyl, substituted
15 or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted aralkyl, substituted or unsubstituted heteroaralkyl, or $C(J)R^{35}$; or R^{31} and R^{32} , together with the atoms to which they are attached, form substituted or unsubstituted cycloalkyl ring, a substituted or unsubstituted heterocyclic ring or a substituted or unsubstituted
20 heteroaryl ring;

J is O, S or NR^{40} ;

R^{35} is hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocyclyl,
25 substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted alkoxy, substituted or unsubstituted aralkoxy, substituted or unsubstituted alkylamino, substituted or unsubstituted dialkylamino, substituted or unsubstituted arylalkylamino, or substituted or unsubstituted diarylamino;

-432-

R⁴⁰ is hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl;

where the alkyl, alkenyl, alkynyl, cycloalkyl, heterocyclyl, alkylene, alkenylene, alkynylene, aryl, heteroaryl, aralkyl, aralkenyl, aralkynyl, heteroaralkyl, heteroaralkenyl and heteroaralkynyl moieties of R¹, R², R³, R⁵, R⁶, R⁷, R⁸, R⁹ and R¹⁰ are unsubstituted or substituted with one or more substituents, in one embodiment one to three or four substituents, each independently selected from Q¹, where Q¹ is halo, pseudohalo, hydroxy, oxo, thia, nitrile, nitro, formyl, mercapto, amino, hydroxyalkyl, hydroxyalkylaryloxy, hydroxyaryl, hydroxyalkylaryl, hydroxycarbonyl, hydroxycarbonylalkyl, alkyl, haloalkyl, polyhaloalkyl, aminoalkyl, diaminoalkyl, alkenyl containing 1 to 2 double bonds, alkynyl containing 1 to 2 triple bonds, cycloalkyl, cycloalkylalkyl, heterocyclyl, heterocyclylalkyl, aryl, diaryl, hydroxyaryl, alkylaryl, heteroaryl, aralkyl, aralkenyl, aralkynyl, alkylaralkyl, heteroarylalkyl, trialkylsilyl, dialkylarylsilyl, alkyl diarylsilyl, triarylsilyl, alkylidene, arylalkylidene, alkylcarbonyl, alkylarylcarbonyl, arylcarbonyl, heterocyclylcarbonyl, heteroarylcarbonyl, alkoxycarbonyl, alkoxycarbonylalkyl, alkoxycarbonylaryloxy, aryloxycarbonyl, aryloxycarbonylalkyl, heterocyclylcarbonylalkylaryl, aralkoxycarbonyl, aralkoxycarbonylalkyl, arylcarbonylalkyl, aminocarbonyl, alkylaminocarbonyl, dialkylaminocarbonyl, arylaminocarbonyl, diarylaminocarbonyl, arylalkylaminocarbonyl, alkoxy, aryloxy, haloalkoxy, alkoxyaryloxy, alkylaryloxy, diaryloxy, alkylaryloxyalkyl, alkyl diaryloxy, perfluoroalkoxy, alkenyloxy, alkynyloxy, aryloxyalkoxy, aralkoxyaryloxy, alkylarylcycloalkyloxy, heterocycloxy, alkoxyalkyl, alkoxyalkoxyalkyl, alkylheteroaryloxy, alkylcycloalkoxy, cycloalkyloxy, heterocycliloxy, aralkoxy, haloaryloxy, heteroaryloxy, alkylheteroaryloxy, alkoxycarbonylheterocycloxy, alkylcarbonylaryloxy, alkylcarbonyloxy,

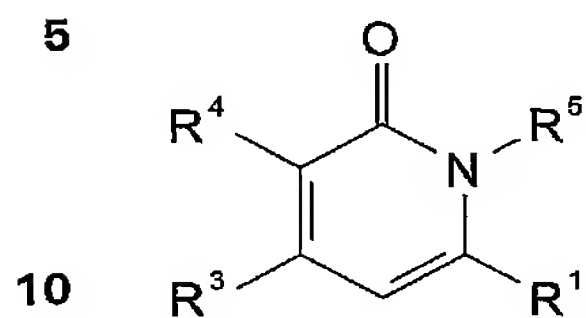
-433-

- arylcarbonyloxy, aralkylcarbonyloxy, alkoxycarbonyloxy, aryloxycarbon-
 yloxy, alkoxyaryloxy, aralkoxycarbonyloxy, ureido, alkylureido, aryl-
 ureido, amino, aminoalkyl, alkylaminoalkyl, dialkylaminoalkyl, aryl-
 aminoalkyl, diarylaminoalkyl, alkylarylaminoalkyl, alkylamino, dialkyl-
 5 amino, haloalkylamino, haloalkylarylamino, arylamino, diarylamino, alkyl-
 arylamino, aralkylamino, alkylcarbonylamino, aralkylcarbonylamino,
 haloalkylcarbonylamino, alkoxycarbonylamino, aralkoxycarbonylamino,
 arylcarbonylamino, arylcarbonylaminoalkyl, aryloxycarbonylaminoalkyl,
 aryloxyarylcarbonylamino, aryloxycarbonylamino, alkylenedioxyalkyl,
 10 dialkylalkylenedioxyalkyl, alkylsulfonylamino, arylsulfonylamino, azido,
 dialkylphosphonyl, alkylarylphosphonyl, diarylphosphonyl, alkylthio, aryl-
 thio, perfluoroalkylthio, hydroxycarbonylalkylthio, thiocyano,
 isothiocyano, alkylsulfinyl, alkylsulfonyl, arylsulfinyl, arylsulfonyl,
 aminosulfonyl, alkylaminosulfonyl, dialkylaminosulfonyl,
 15 arylaminosulfonyl, diarylaminosulfonyl or alkylarylaminosulfonyl; or two
 Q^1 groups, which substitute atoms in a 1,2 or 1,3 arrangement, together
 form alkylenedioxy (*i.e.*, $-O-(CH_2)_z-O-$), thioalkylenoxy (*i.e.*,
 $-S-(CH_2)_z-O-$) or alkylenedithioxy (*i.e.*, $-S-(CH_2)_z-S-$) where z is 1 or 2; and
 each Q^1 is independently unsubstituted or substituted with one or
 20 more substituents, in one embodiment one to three or four substituents,
 each independently selected from Q^2 , where Q^2 is halo, pseudohalo,
 hydroxy, oxo, thia, nitrile, nitro, formyl, mercapto, amino, hydroxyalkyl,
 hydroxyaryl, hydroxycarbonyl, alkyl, haloalkyl, polyhaloalkyl, aminoalkyl,
 diaminoalkyl, alkenyl containing 1 to 2 double bonds, alkynyl containing
 25 1 to 2 triple bonds, cycloalkyl, heterocyclyl, aryl, heteroaryl, aralkyl,
 aralkenyl, aralkynyl, alkoxycarbonyl, aryloxycarbonyl, aralkoxycarbonyl,
 arylcarbonylalkyl, aminocarbonyl, alkoxy, aryloxy, aralkoxy,
 alkylenedioxy, amino, aminoalkyl, dialkylamino, arylamino, diarylamino,
 alkylamino, dialkylamino, haloalkylamino, arylamino, diarylamino, alkyl-

-434-

arylamino, aralkylamino, alkoxycarbonylamino, arylcarbonylamino, alkylthio or arylthio.

139. The compound of claim 1 that has formula II:



or a pharmaceutically acceptable derivative thereof.

15 140. The compound of claim 91, wherein each Ar is independently substituted or unsubstituted heteroaryl.

(1/78)

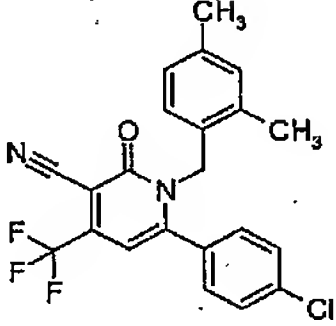
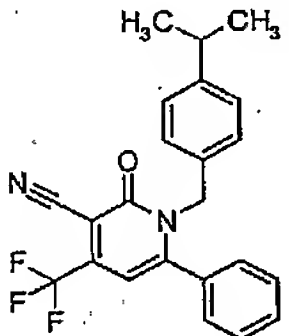
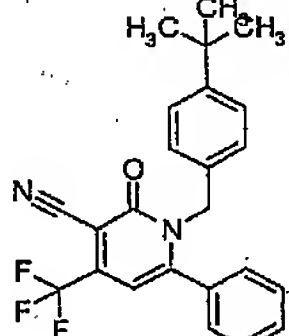
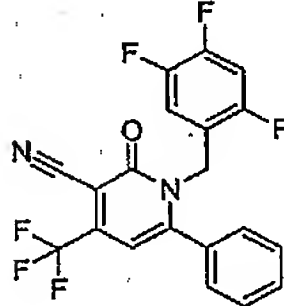
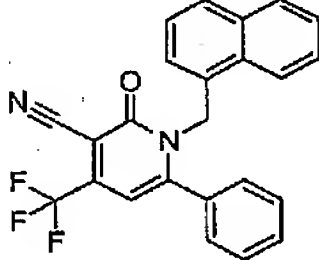
Serial No.	Structure	Ki(a)	Ki(b)	EC50(a)	%Eff(a)	EC50(b)	%Eff(b)
1		B1	B1	III	B	III	B
2		D1	D1	IV	A	IV	B
3		NC	NC	NC	A	NC	A
4		A1	A1	III	B	III	B
5		B1	B1	IV	A	IV	B

FIG. 1A

(2/78)

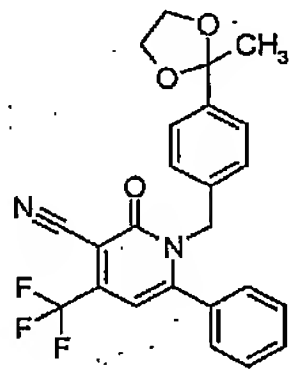
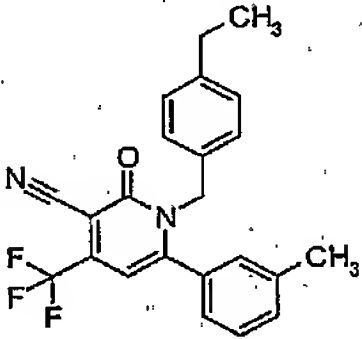
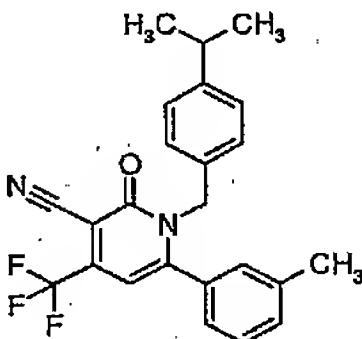
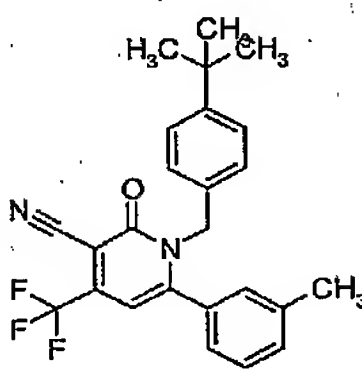
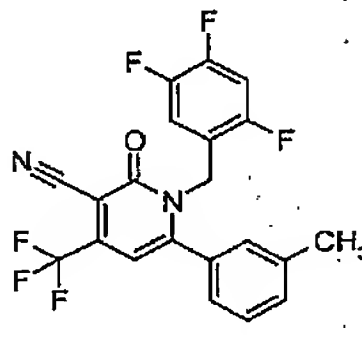
6		NC	NC	NC	NC	NC	NC
7		B1	B1	III	B	III	B
8		D1	D1	III	A	IV	A
9		NC	NC	NC	NC	NC	NC
10		A1	A1	III	B	III	B

FIG. 1B

(3/78)

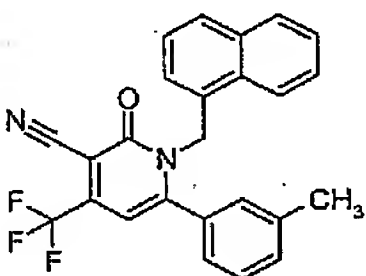
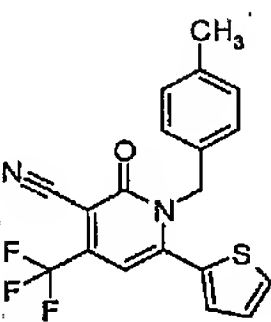
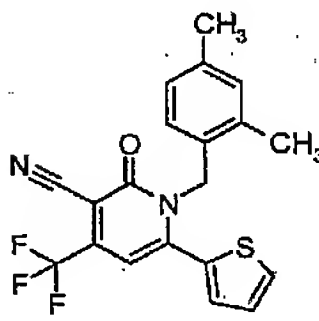
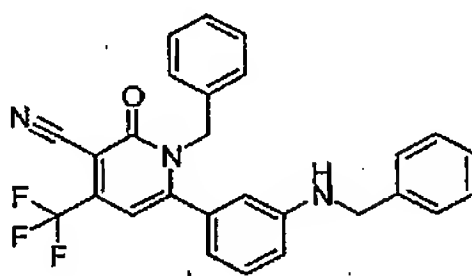
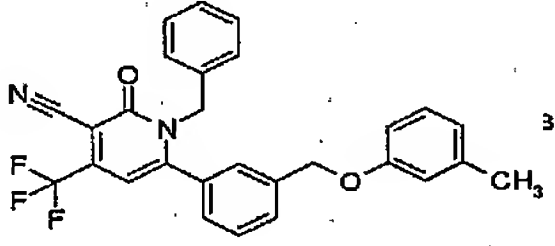
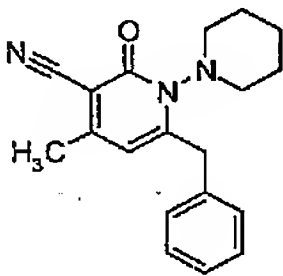
11		B1	B1	III	B	IV	B
12		B1	A1	III	B	III	B
13-1		A1	A1	III	B	III	B
13-2		A1	A1	III	B	III	C
14		C1	B1	III	B	III	B
15		31	B1	IV	B	IV	B
16		NC	NC	NC	NC	NC	NC

FIG. 1C

(4/78)

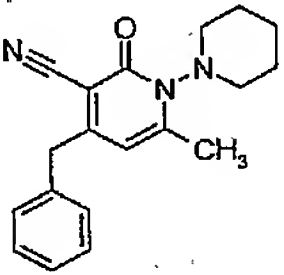
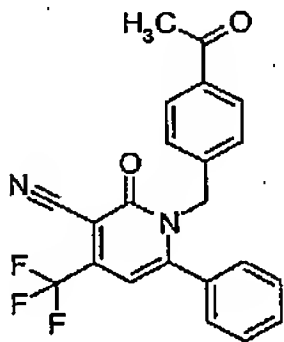
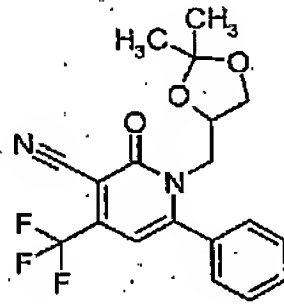
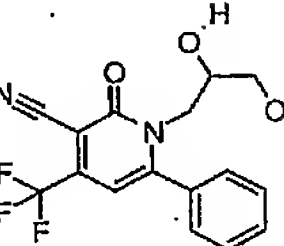
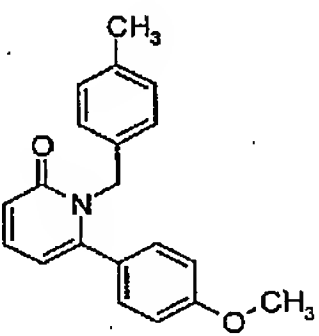
17		D1	NC	NC	NC	NC	NC
18		C1	B1	IV	B	IV	B
19		NC	D1	III	A	NC	B
20		NC	NC	NC	NC	NC	NC
21		NC	NC	NC	NC	NC	NC

FIG. 1D

(5/78)

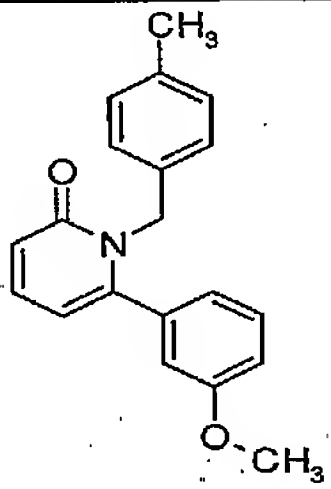
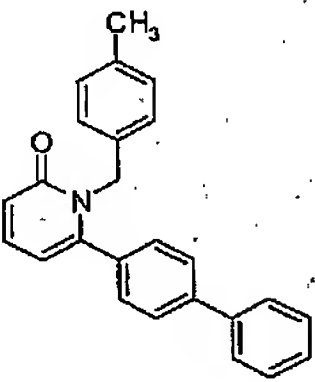
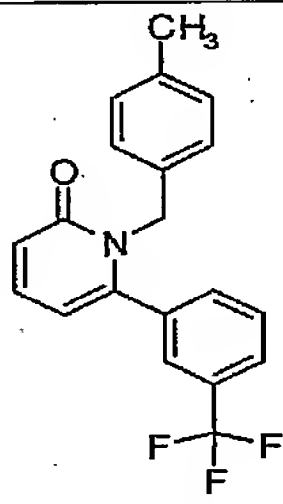
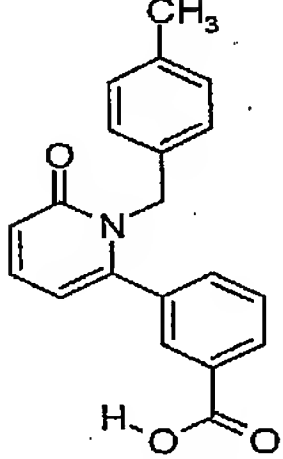
22	 <chem>Cc1ccc(cc1)CN2C(=O)C=CC=C2c3ccc(OC)cc3</chem>	NC	NC	NC	NC	NC	NC
23	 <chem>Cc1ccc(cc1)CN2C(=O)C=CC=C2c3ccc(cc3-c4ccccc4)</chem>	NC	NC	NC	NC	NC	NC
24	 <chem>Cc1ccc(cc1)CN2C(=O)C=CC=C2c3ccc(C(F)(F)F)cc3</chem>	NC	NC	NC	NC	NC	NC
25	 <chem>Cc1ccc(cc1)CN2C(=O)C=CC=C2c3ccc(C(=O)O)cc3</chem>	NC	NC	NC	NC	NC	NC

FIG. 1E

(6/78)

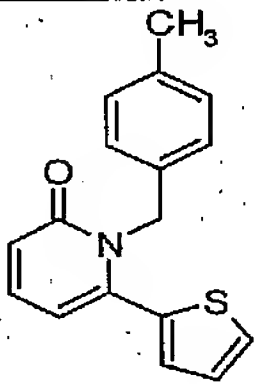
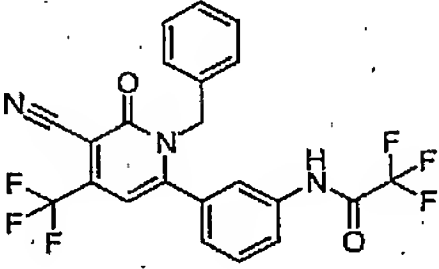
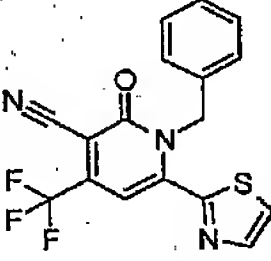
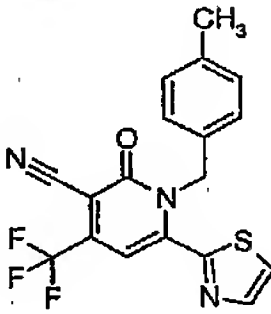
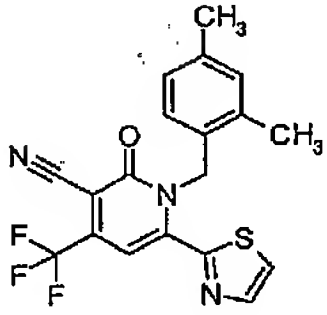
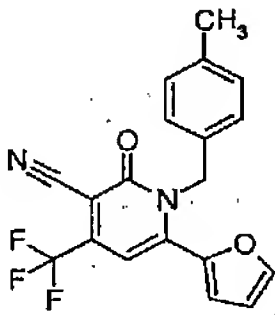
26		NC	NC	NC	NC	NC	NC
27		B1	B1	IV	B	IV	C
28		C1	B1	IV	A	IV	A
29		B1	A1	III	B	III	C
30-1		B1	A1	III	B	III	D
30-2		B1	A1	III	B	III	C
31		B1	B1	III	B	IV	C

FIG. 1F

(7/78)

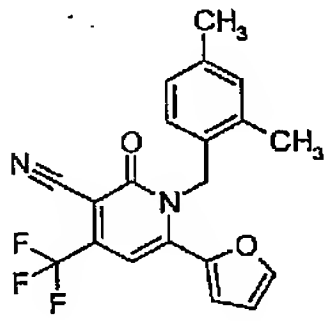
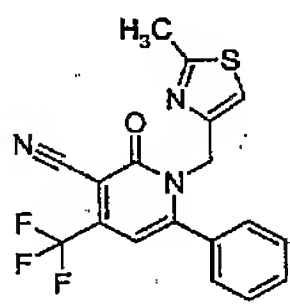
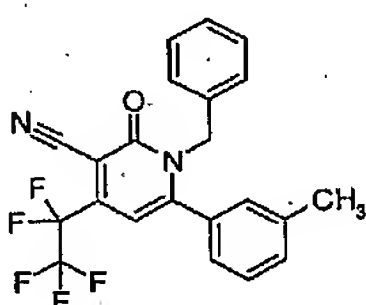
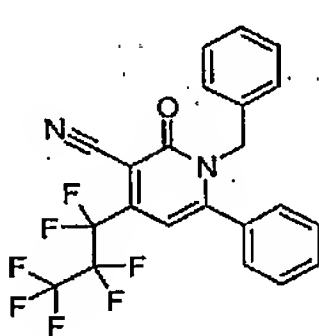
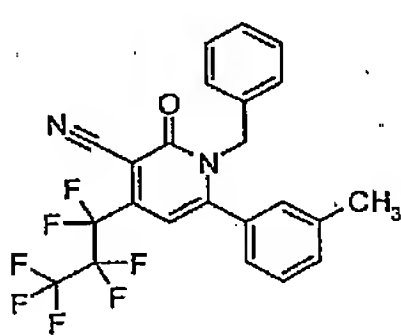
32-1		B1	B1	III	A	III	B
32-2		B1	A1	III	B	III	B
33		C1	B1	NC	B	IV	C
34		B1	A1	III	B	IV	B
35		D1	B1	IV	B	IV	B
36		B1	B1	IV	B	IV	B

FIG. 1G

(8/78)

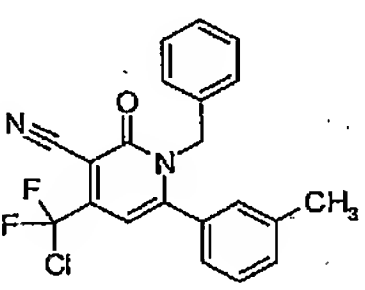
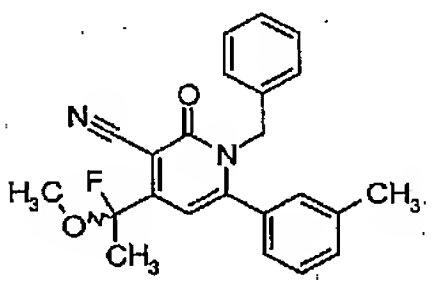
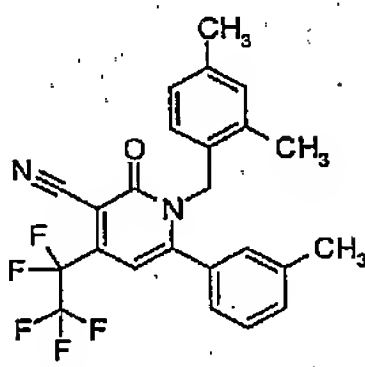
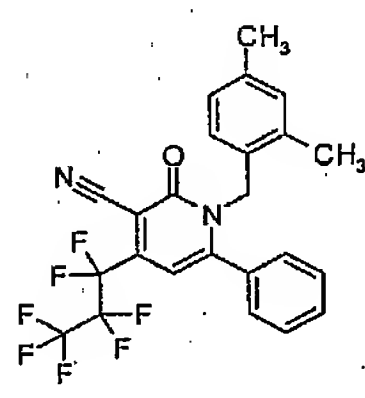
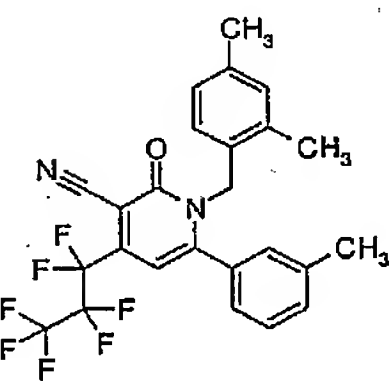
37		B1	A1	III	B	III	C
38		D1	C1	IV	A	NC	B
39		A1	A1	III	A	III	B
40		B1	B1	III	B	III	B
41		B1	B1	III	B	III	B

FIG. 1H

(9/78)

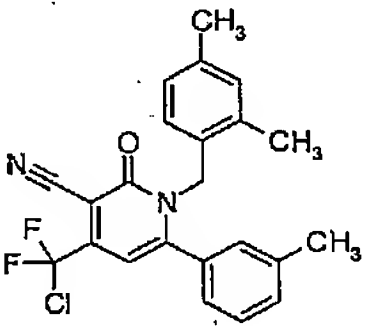
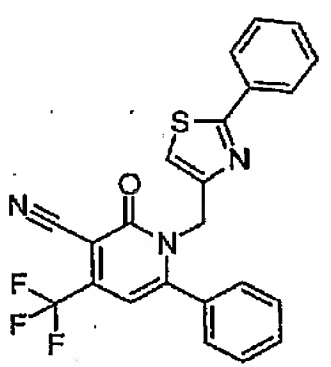
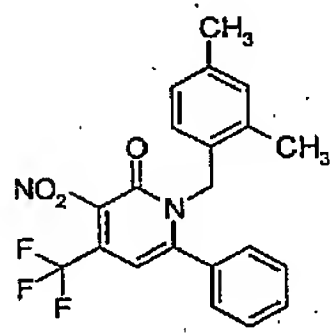
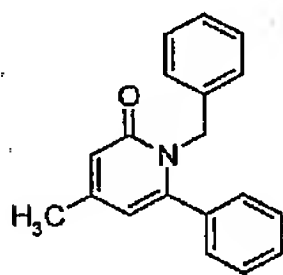
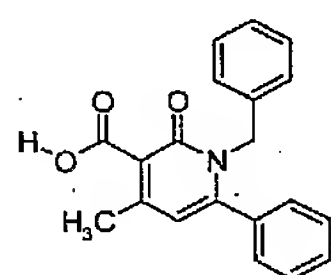
42		A1	A1	III	B	III	B
43		NC	NC	IV	A	IV	A
44		NC	NC	NC	NC	NC	NC
45		NC	NC	NC	NC	NC	NC
46		NC	NC	NC	NC	NC	NC

FIG. 11

(10/78)

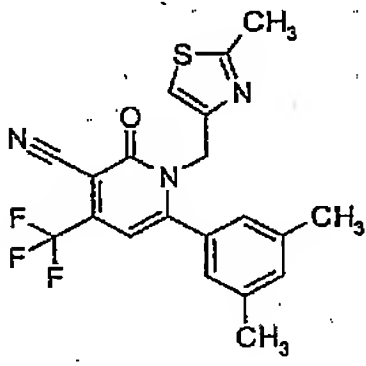
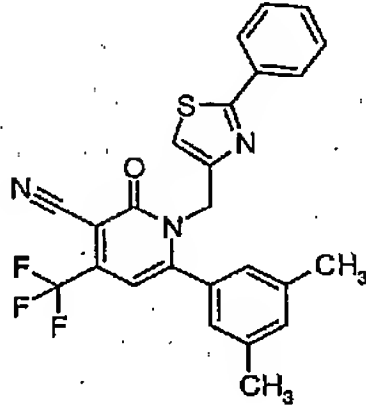
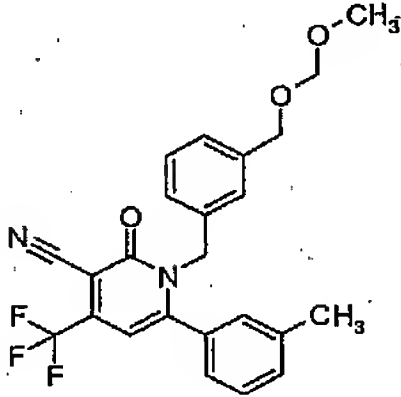
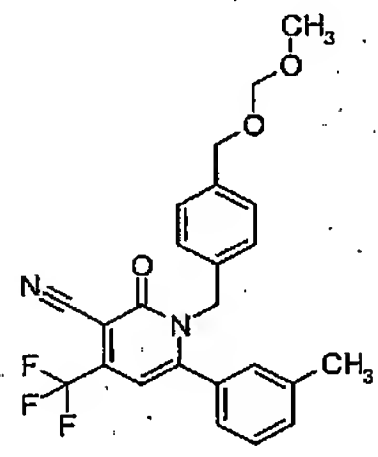
47		B1	B1	IV	C	IV	C
48		B1	B1	IV	A	IV	B
49		NC	NC	NC	NC	NC	NC
50		NC	D1	NC	NC	IV	A

FIG. 1J

(11/78)

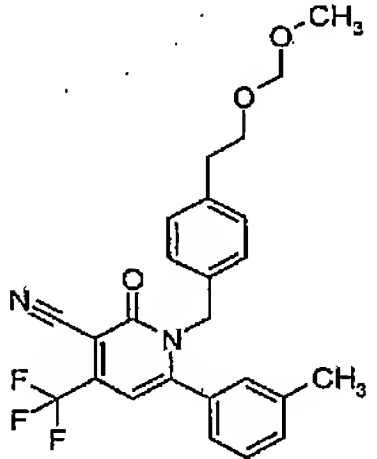
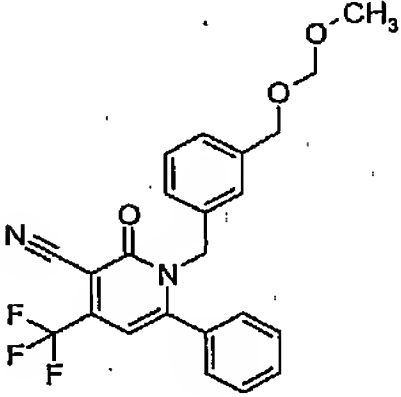
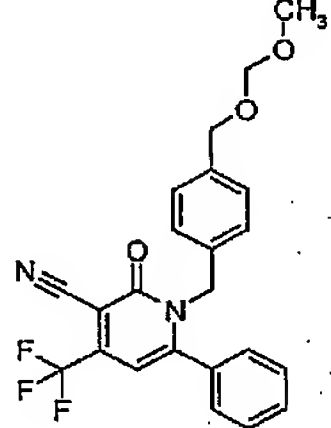
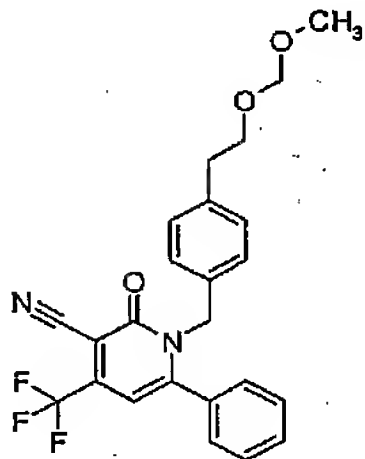
51		NC	NC	NC	NC	IV	A
52		NC	NC	NC	NC	NC	NC
53		D1	D1	NC	NC	NC	NC
54		NC	NC	NC	NC	NC	NC

FIG. 1K

(12/78)

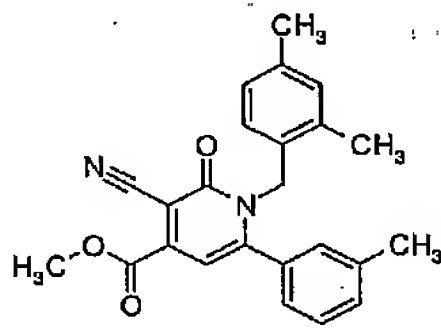
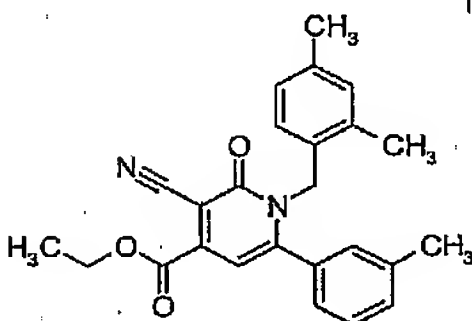
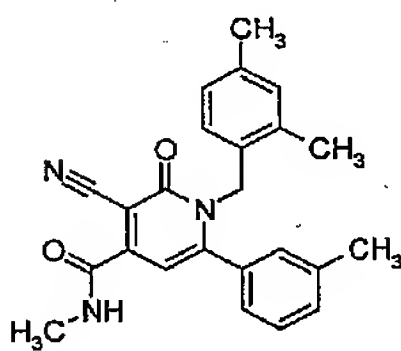
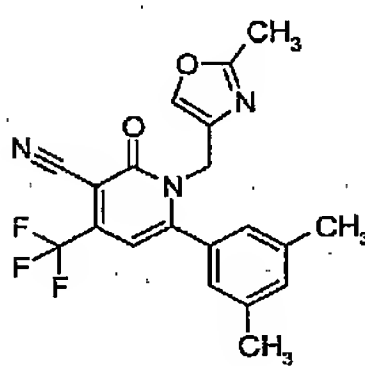
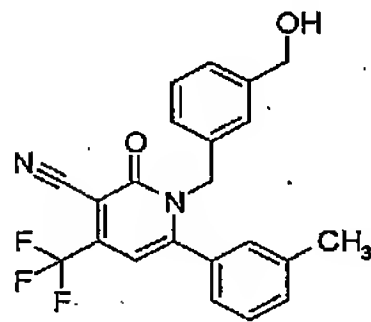
55		D1	D1	IV	A	IV	A
56		C1	B1	NC	A	NC	B
57		D1	D1	NC	A	NC	A
58		C1	B1	IV	B	IV	B
59		NC	IV	NC	NC	NC	NC

FIG. 1L

(13/78)

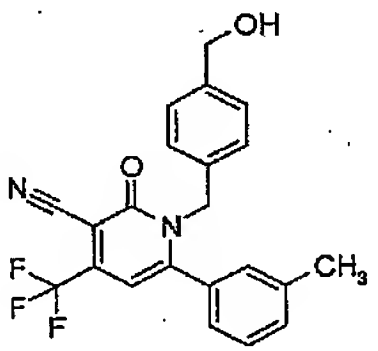
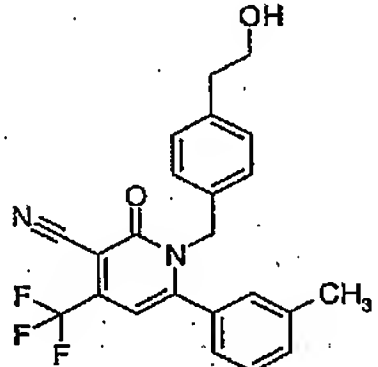
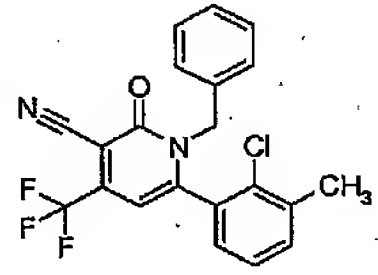
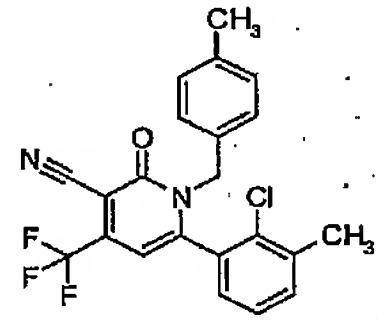
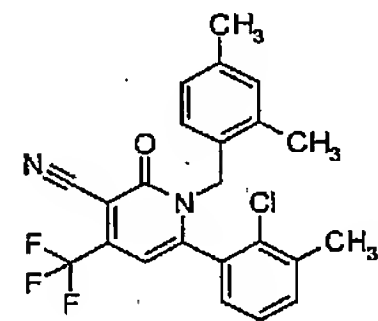
60		D1	D1	NC	B	IV	B
61		NC	NC	NC	NC	NC	NC
62		B1	A1	III	C	III	C
63		A1	A1	III	C	III	B
64		B1	A1	III	B	III	B

FIG. 1M

(14/78)

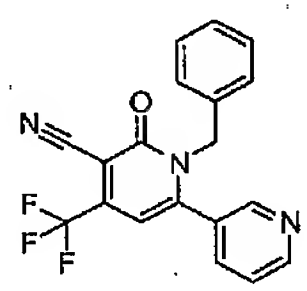
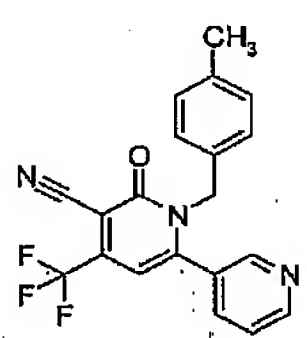
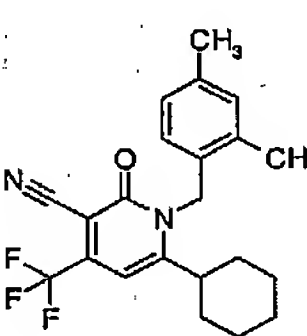
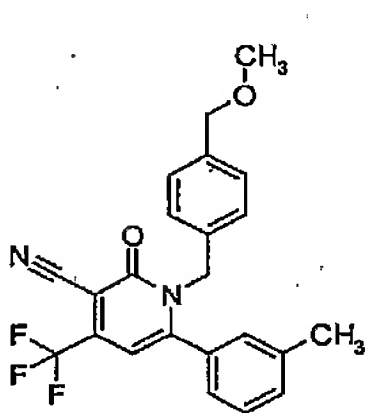
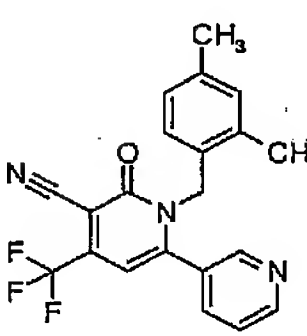
65		NC	D1	IV	A	IV	A
66		D1	B1	IV	B	IV	B
67		A1	A1	III	B	III	C
68		D1	B1	IV	A	IV	B
69		B1	B1	IV	B	III	B

FIG. 1N

(15/78)

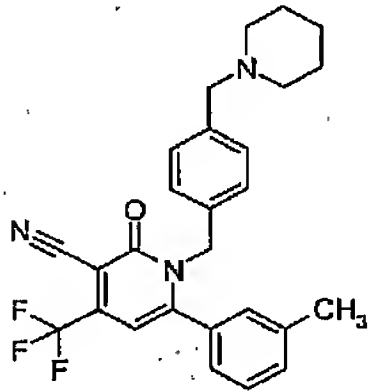
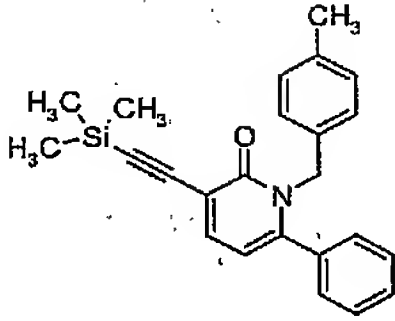
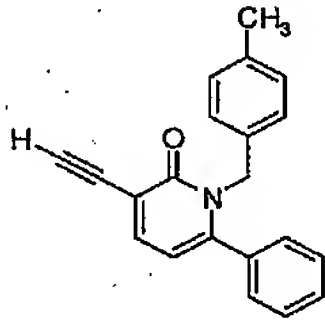
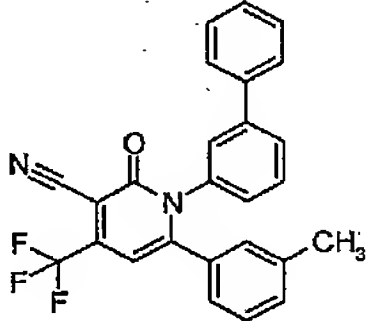
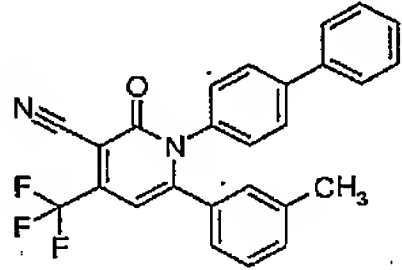
70		D1	D1	NC	NC	NC	NC
71		NC	NC	NC	NC	NC	NC
72		NC	NC	NC	NC	NC	NC
73		D1	B1	IV	A	IV	B
74		D1	D1	NC	NC	IV	A

FIG. 10

(16/78)

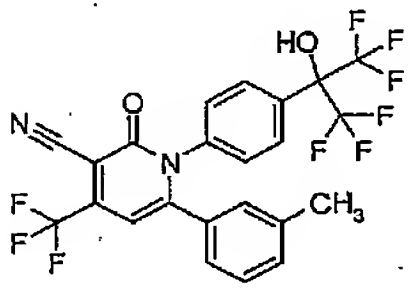
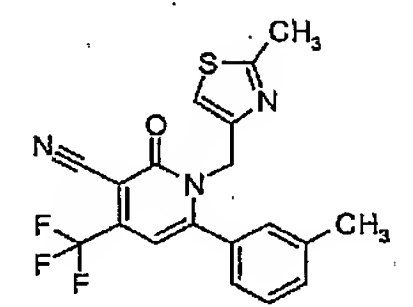
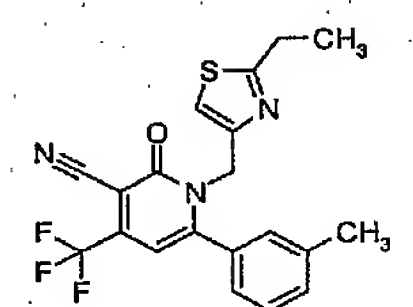
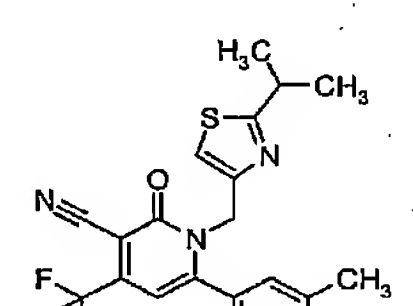
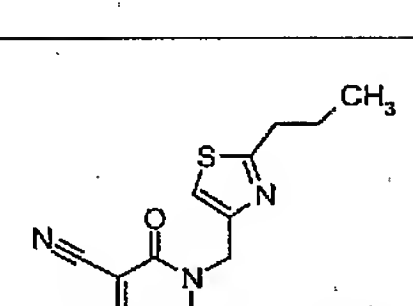
75		D1	D1	IV	A	IV	B
76		B1	B1	IV	C	IV	C
77		B1	A1	III	C	IV	C
78		B1	B1	IV	B	IV	B
79		D1	B1	IV	B	IV	B

FIG. 1P

(17/78)

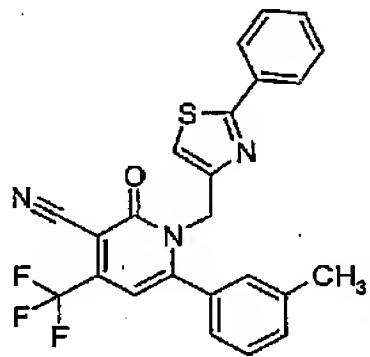
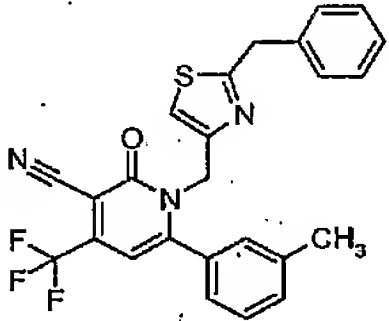
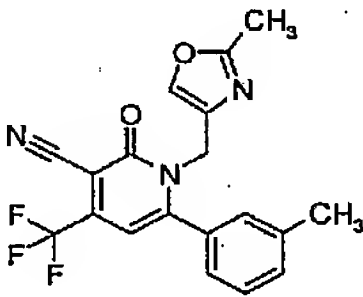
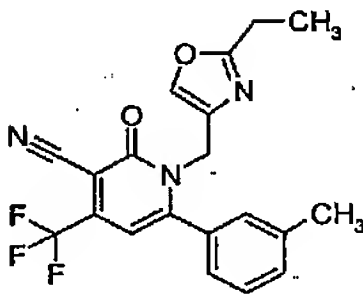
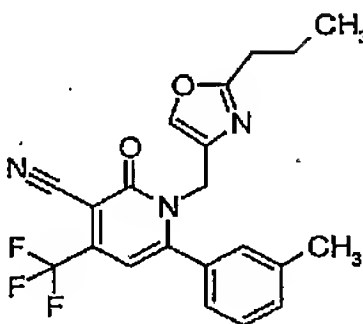
80		NC	D1	IV	A	IV	A
81		NC	NC	NC	NC	IV	A
82		C1	B1	IV	B	IV	B
83		B1	B1	IV	B	IV	B
84		D1	C1	IV	B	NC	B

FIG. 1Q

(18/78)

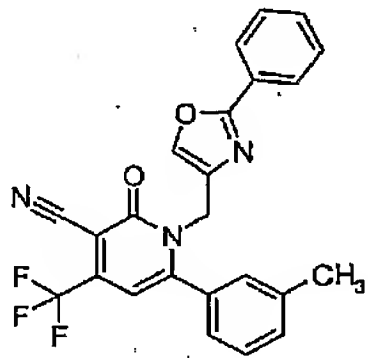
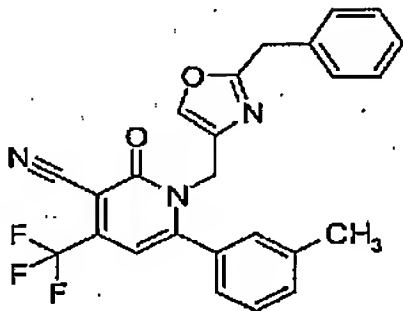
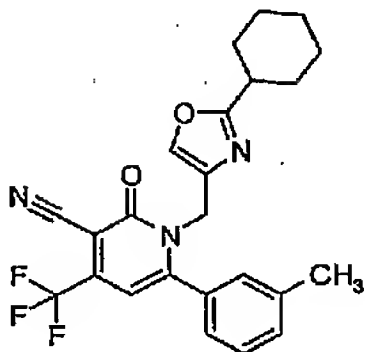
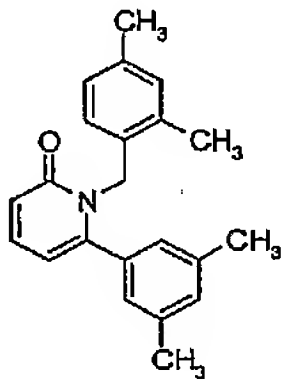
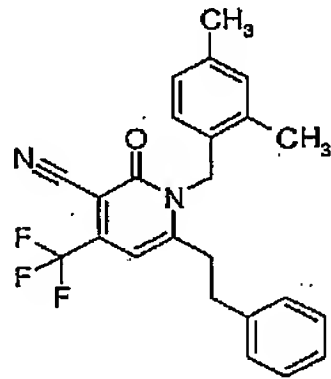
85		NC	D1	IV	A	IV	A
86		NC	D1	NC	NC	NC	NC
87		NC	NC	NC	NC	NC	A
88		NC	NC	NC	NC	NC	NC
89		C1	B1	IV	A	IV	B

FIG. 1R

(19/78)

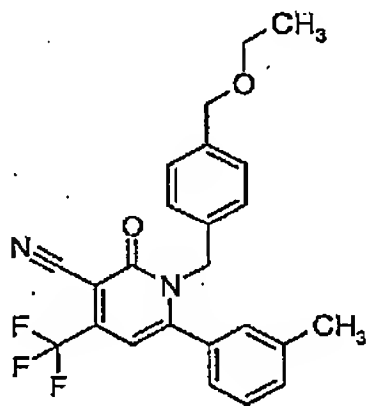
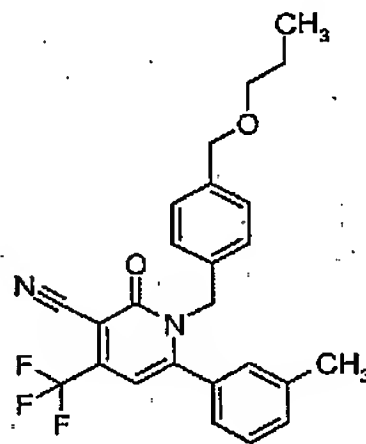
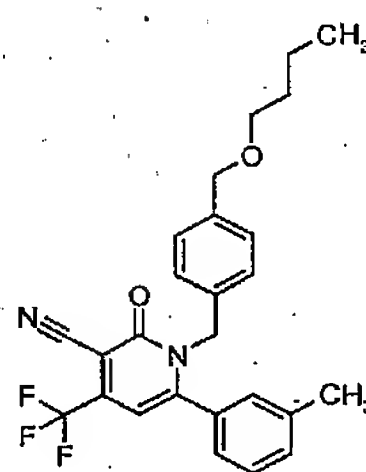
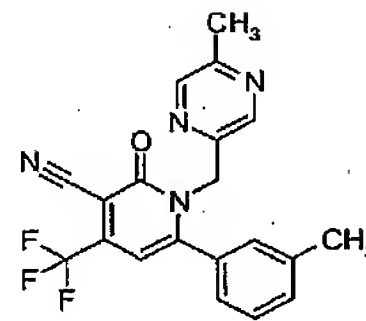
90		NC	D1	IV	A	IV	B
91		D1	D1	NC	NC	IV	A
92		D1	D1	IV	A	III	A
93		B1	B1	IV	C	IV	C

FIG. 1S

(20/78)

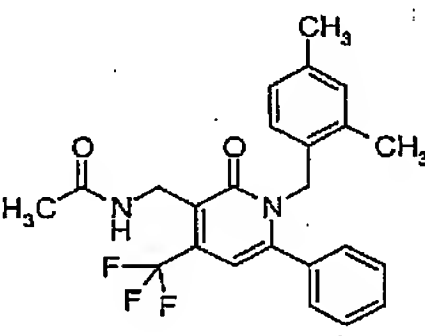
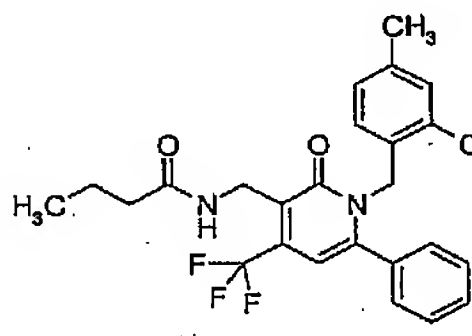
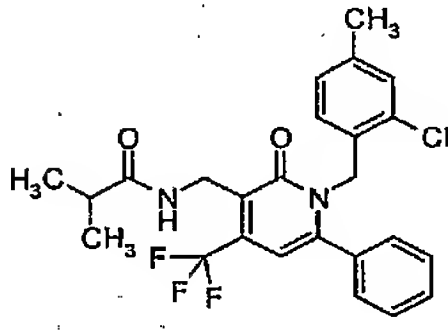
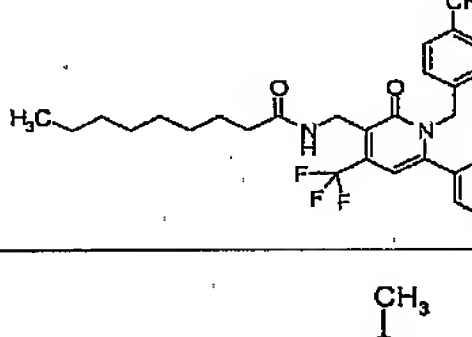
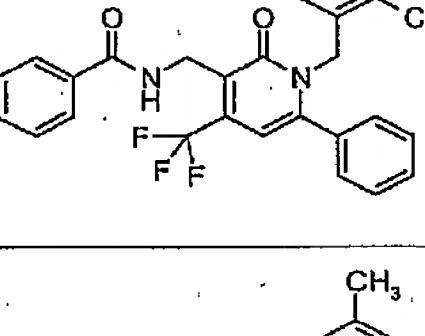
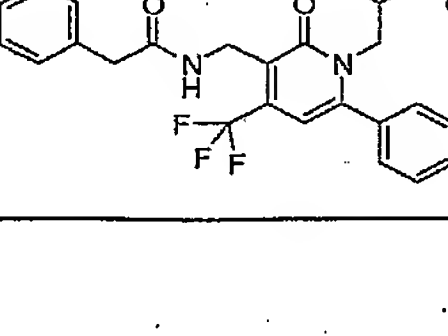
94		D1	C1	IV	A	IV	B
95		D1	D1	NC	NC	NC	NC
96		D1	D1	NC	NC	NC	NC
97		D1	D1	NC	NC	NC	NC
98		D1	D1	IV	A	IV	B
99		D1	D1	NC	NC	NC	NC

FIG. 1T

(21/78)

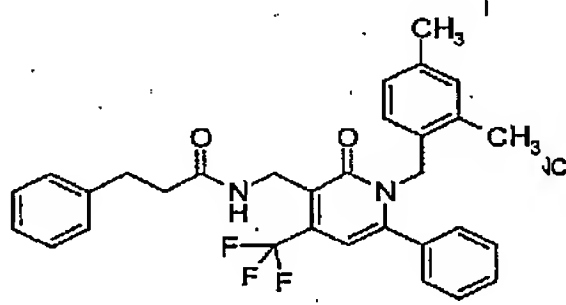
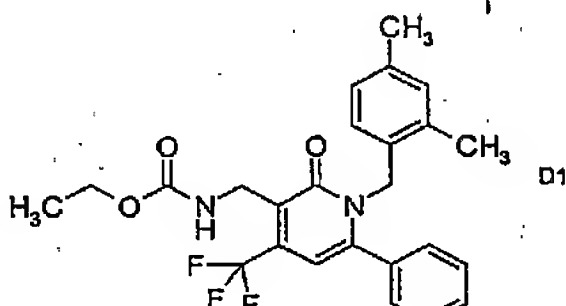
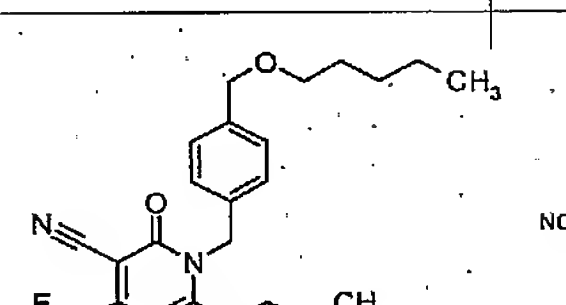
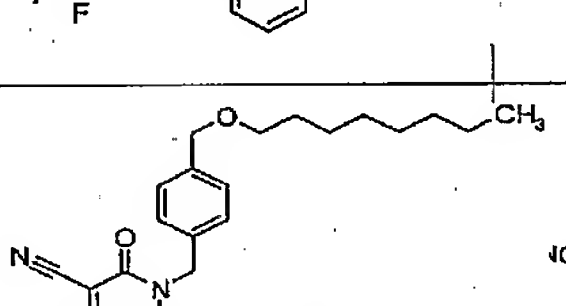
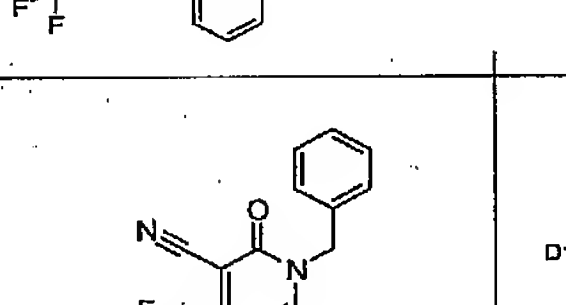
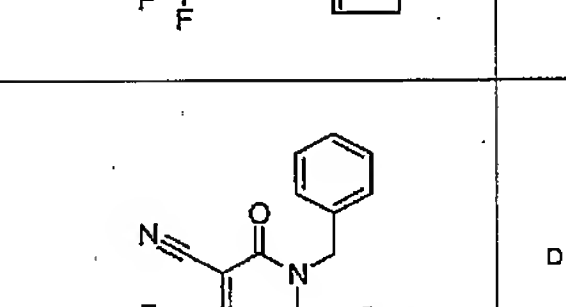
100		NC	NC	NC	NC	NC	
101		B1	IV	A	IV	B	
102		NC	NC	NC	NC	NC	
103		NC	D1	NC	NC	NC	
104		D1	C1	IV	A	IV	B
105		D1	C1	IV	A	IV	B

FIG. 1U

(22/78)

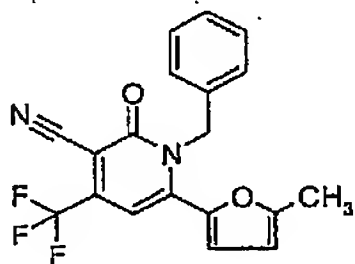
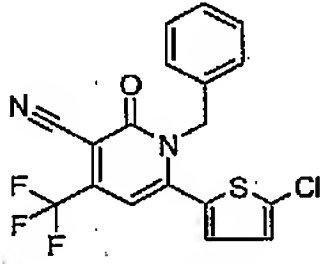
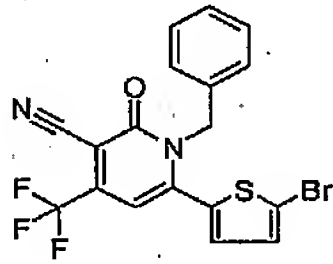
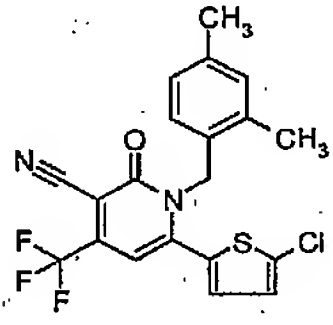
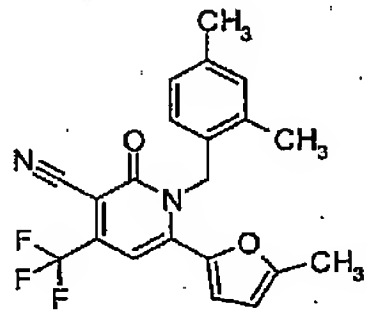
106		D1	B1	IV	B	IV	C
107		D1	D1	IV	B	IV	B
108		D1	D1	NC	B	NC	B
109-1		B1	B1	III	B	III	C
109-2		C1	B1	III	B	III	B
110-1		B1	B1	III	B	III	C
110-2		B1	A1	III	B	III	C

FIG. 1V

(23/78)

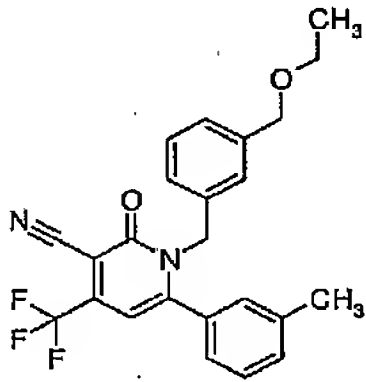
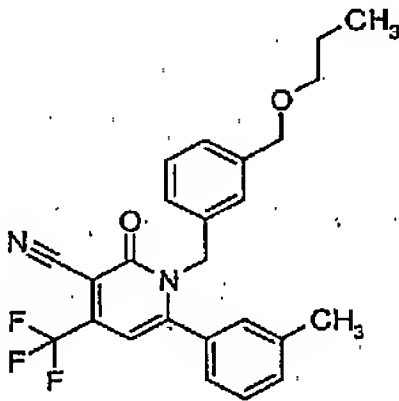
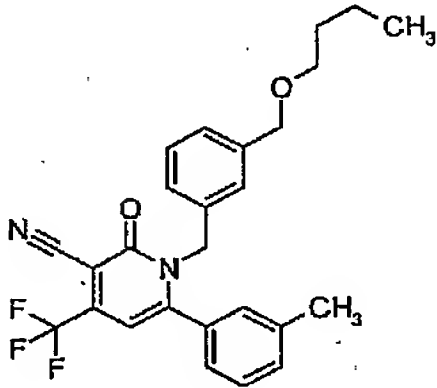
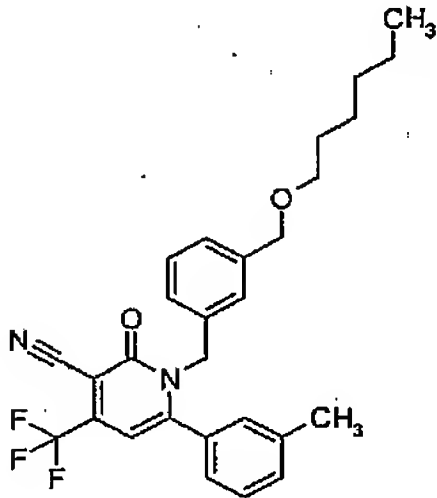
111		NC	NC	NC	NC	NC	NC
112		D1	D1	NC	NC	NC	NC
113		D1	D1	NC	NC	NC	NC
114		NC	NC	NC	NC	NC	NC

FIG. 1W

(24/78)

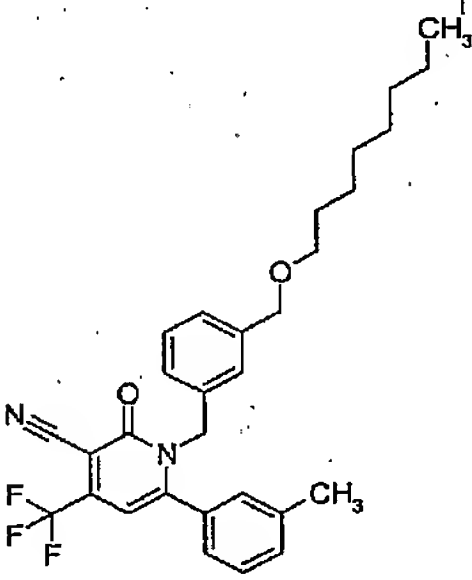
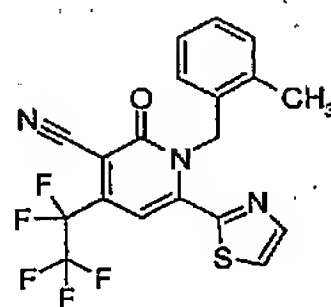
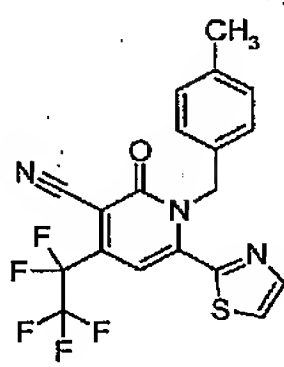
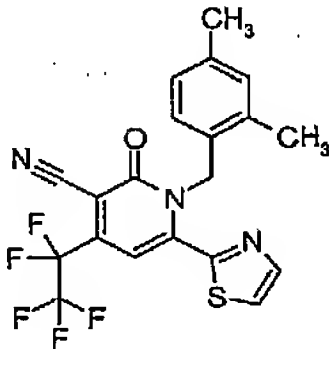
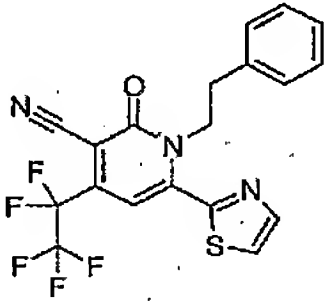
115		NC	NC	NC	NC	NC	NC
116		B1	A1	III	B	III	C
117		B1	B1	III	B	III	C
118		B1	A1	III	B	III	C
119		D1	D1	IV	B	IV	C

FIG. 1X

(25/78)

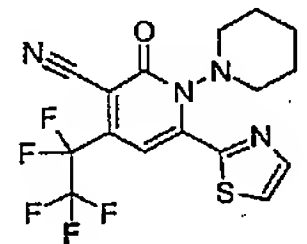
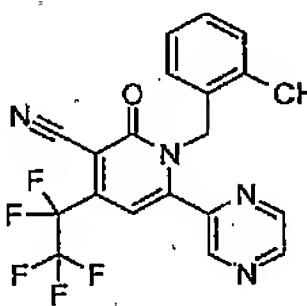
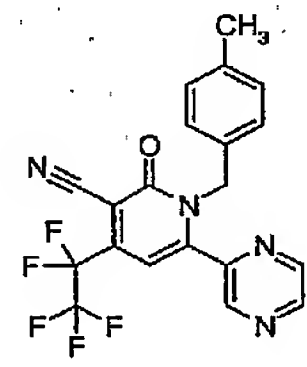
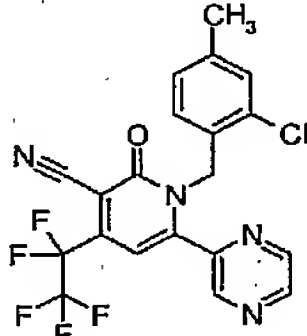
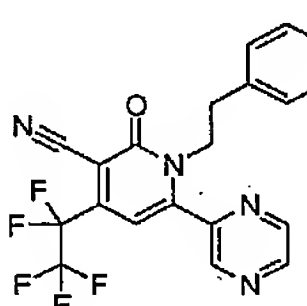
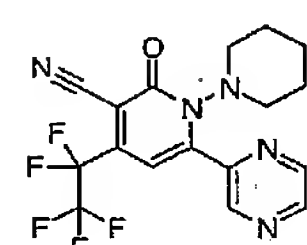
120		D1	D1	NC	NC	NC	NC
121		B1	A1	IV	B	IV	C
122		B1	B1	IV	B	IV	C
123-1		B1	A1	III	B	III	C
123-2		A1	A1	III	B	III	C
124		D1	D1	NC	B	IV	B
125		C	B1	IV	B	IV	B

FIG. 1Y

(26/78)

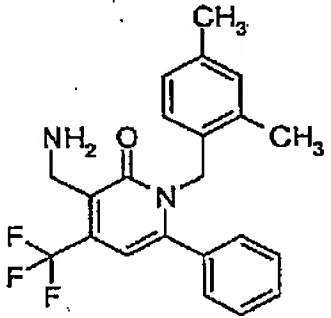
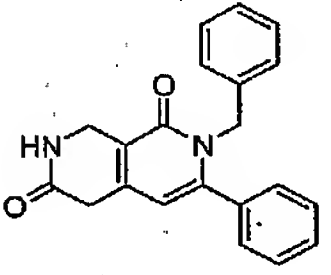
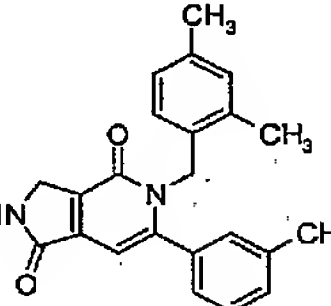
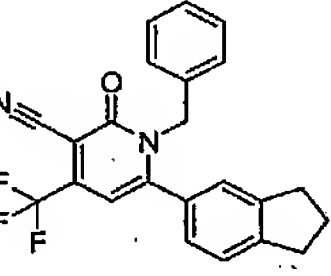
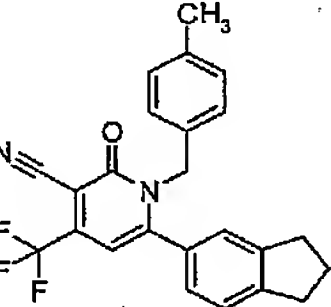
126		C	B1	IV	B	IV	C
127		NC	NC	NC	NC	NC	NC
128		NC	NC	NC	NC	NC	NC
129		B1	B1	III	B	III	B
130		B1	A1	III	B	III	C

FIG. 1Z

(27/78)

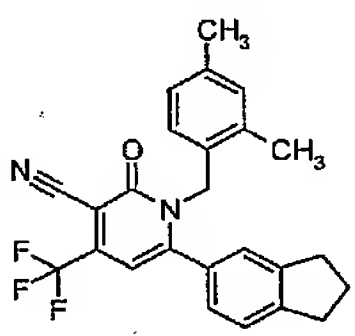
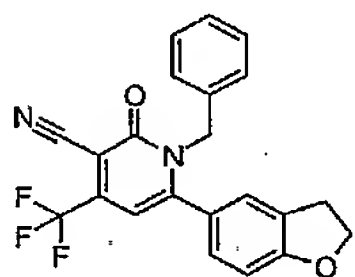
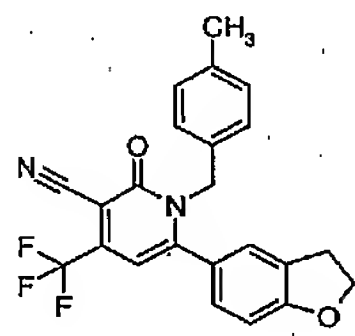
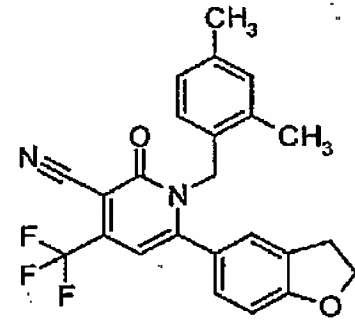
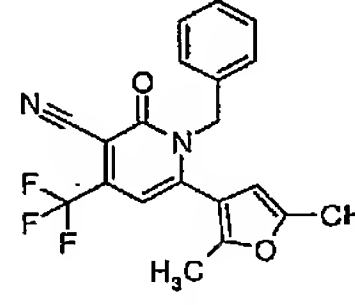
131		B1	A1	III	C	III	C
132		C	B1	III	A	III	A
133		B1	A1	III	C	II	C
134		B1	A1	III	B	III	B
135		B1	B1	IV	B	III	C

FIG. 1AA

(28/78)

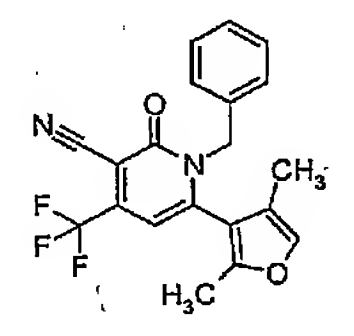
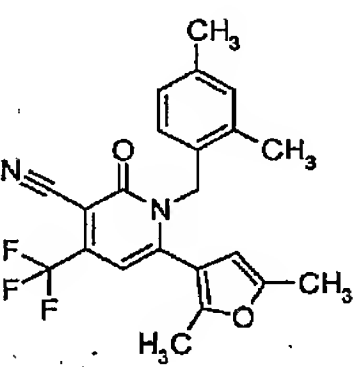
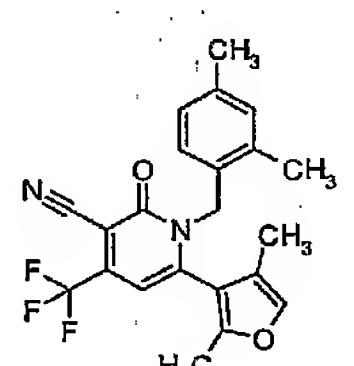
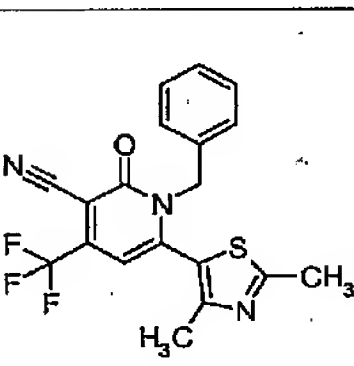
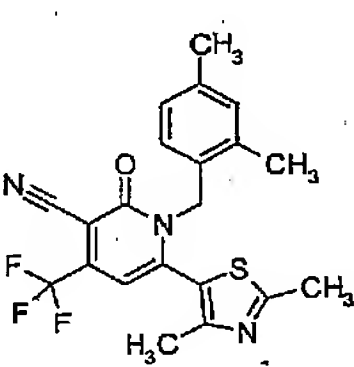
136		D1	D1	IV	A	NC	A
137		A1	A1	II	B	II	C
138		D1	D1	IV	A	IV	B
139		D1	D1	IV	A	NC	NC
140		D1	D1	IV	B	IV	B

FIG. 1AB

(29/78)

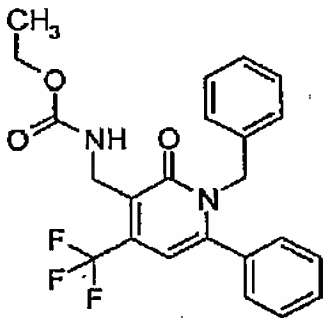
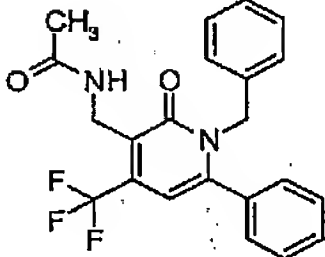
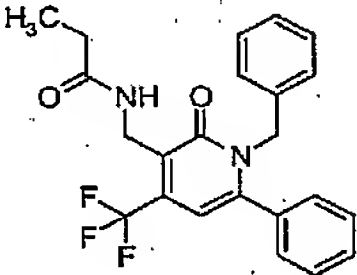
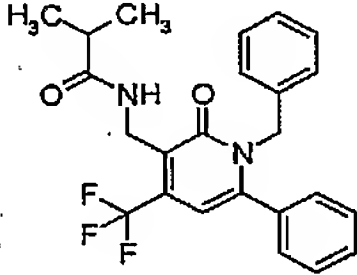
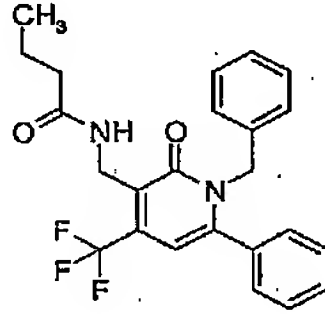
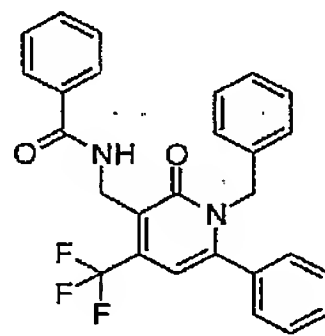
141		NC	D1	NC	NC	IV	A
142		NC	NC	NC	NC	IV	A
143		D1	NC	NC	NC	IV	A
144		NC	D1	NC	NC	IV	A
145		NC	NC	NC	NC	NC	NC
146		D1	D1	NC	NC	NC	NC

FIG. 1AC

(30/78)

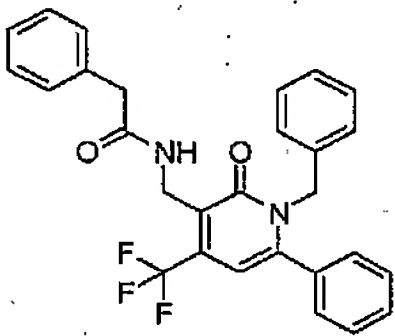
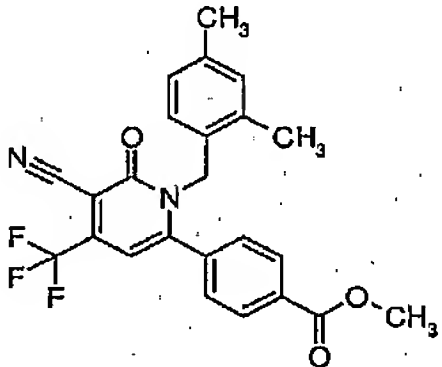
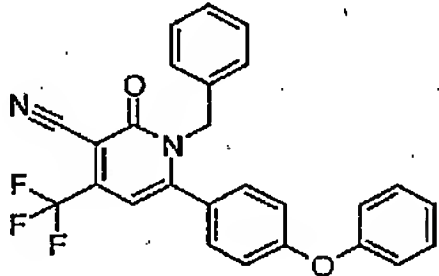
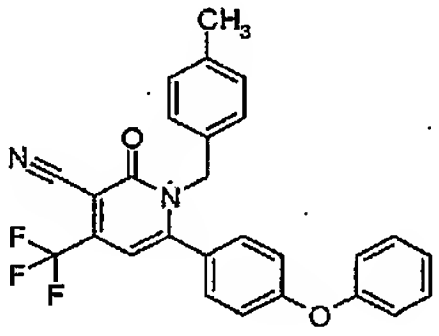
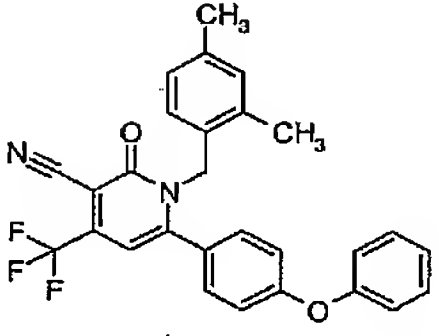
147		D1	D1	NC	NC	IV	A
148		B1	B1	IV	B	IV	B
149		A1	A1	III	B	II	C
150		NC	NC	II	C	II	C
151		A1	A1	II	C	II	C

FIG. 1AD

(31/78)

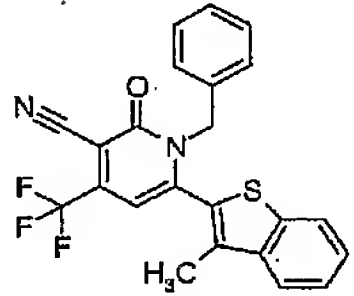
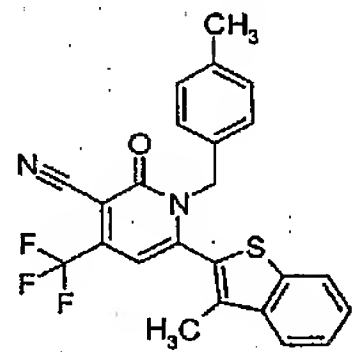
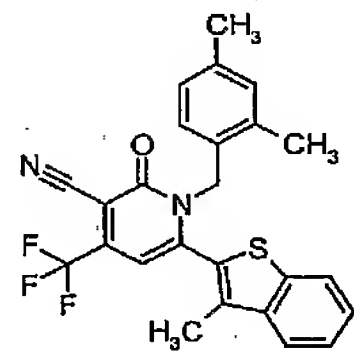
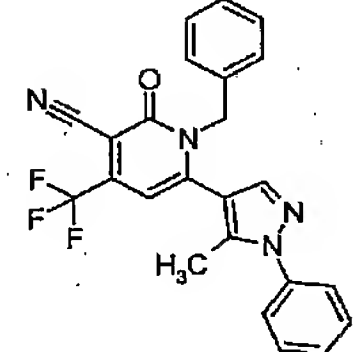
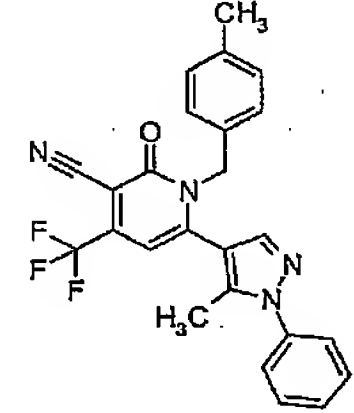
152		C	C1	IV	A	IV	A
153		B1	B1	III	B	III	B
154		B1	B1	III	B	III	B
155		D1	C	IV	B	IV	B
156		B1	A1	III	B	III	C

FIG. 1AE

(32/78)

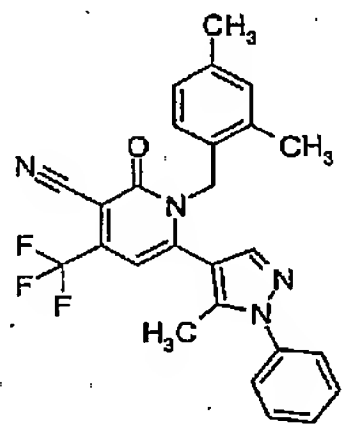
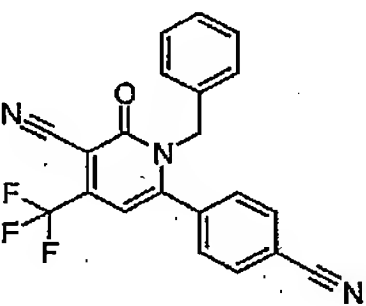
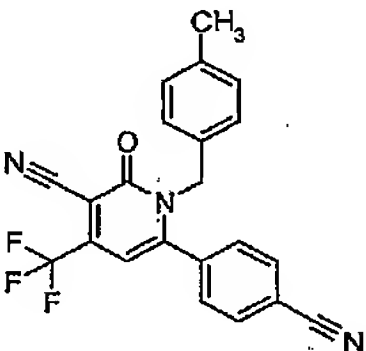
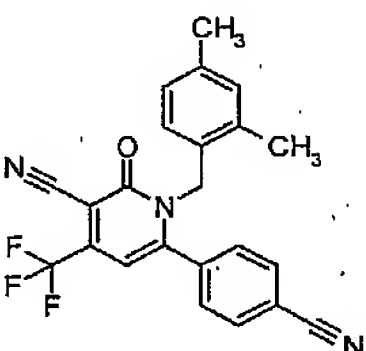
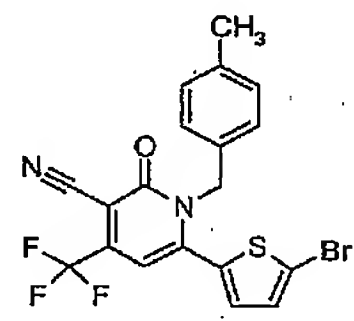
157		A1	A1	III	B	III	C
158		D1	D1	IV	A	IV	B
159		B1	B1	IV	B	IV	C
160		B1	A1	III	B	III	C
161		B1	B1	III	B	III	A

FIG. 1AF

(33/78)

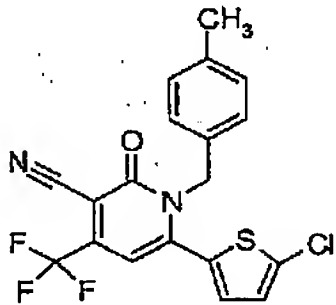
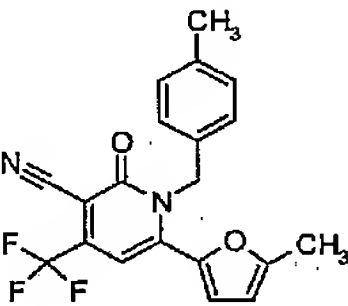
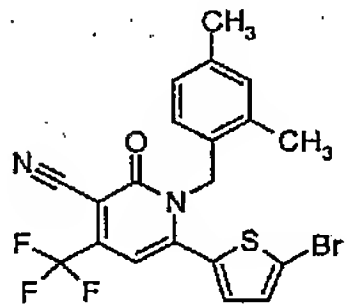
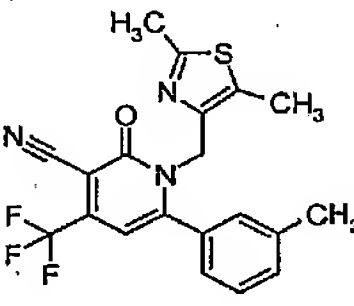
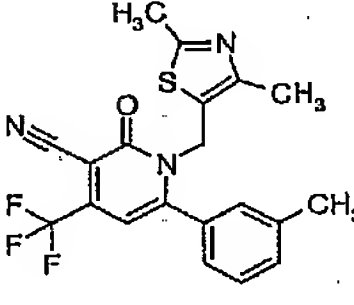
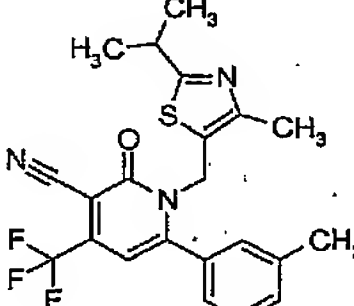
162		B1	B1	III	C	III	B
163		B1	A1	III	B	III	B
164		D1	D1	III	B	III	B
165		B1	A1	III	B	III	B
166		C1	C1	IV	B	IV	A
167		D1	D1	IV	A	NC	NC

FIG. 1AG

(34/78)

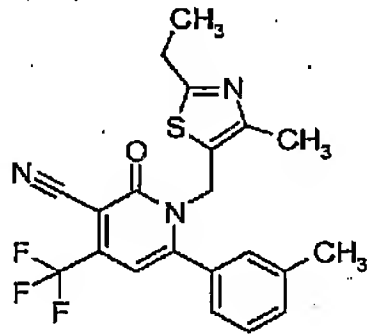
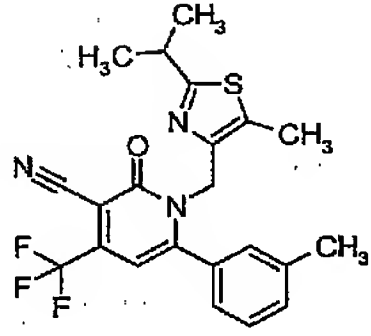
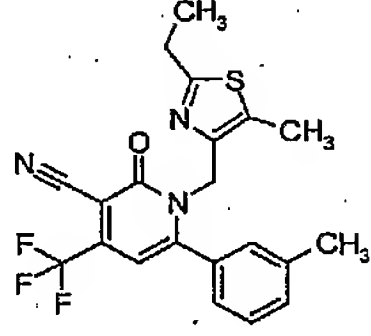
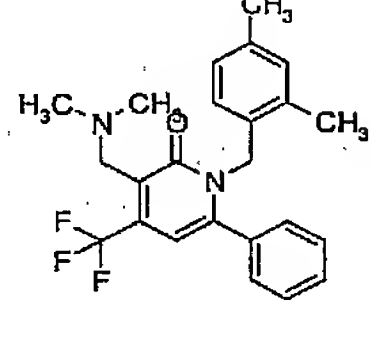
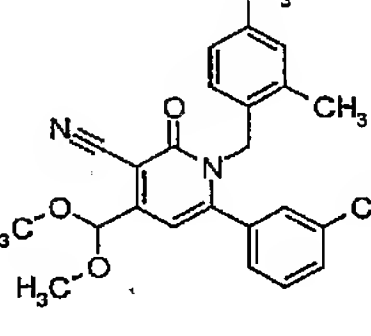
168		C1	C1	IV	B	IV	A
169		B1	B1	III	B	III	B
170		B1	A1	III	B	III	B
171		B1	B1	III	B	III	B
172		A1	A1	III	B	III	B

FIG. 1AH

(35/78)

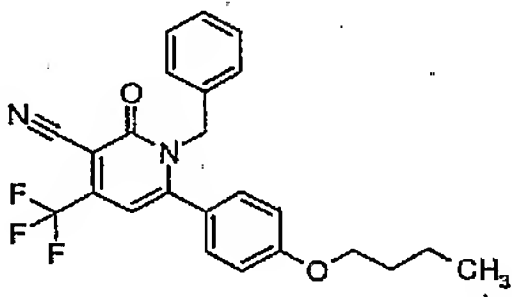
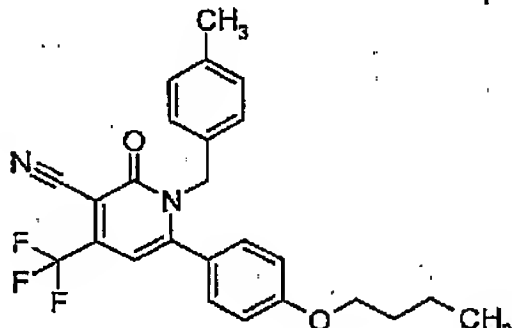
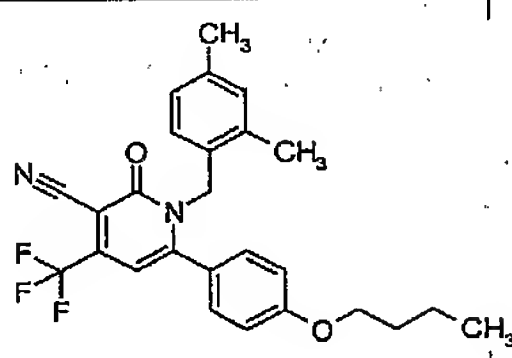
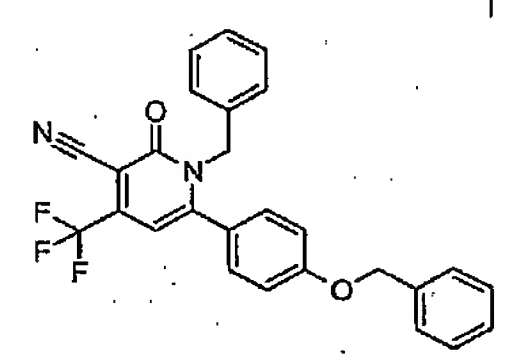
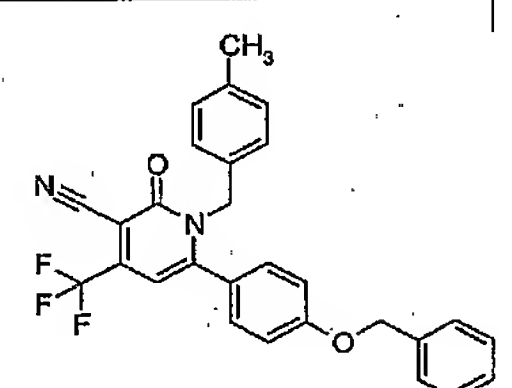
173	 <chem>N#Cc1cc(C(F)(F)F)c(NCc2ccccc2)c(c1)C3=CC=C(C=C3)OCCCH3</chem>	C	B1	III	B	III	B
174	 <chem>Cc1ccc(CCNc2cc(C(F)(F)F)c(N#C)c2C3=CC=C(C=C3)OCCCH3)cc1</chem>	B1	B1	III	B	III	B
175	 <chem>Cc1cc(CCNc2cc(C(F)(F)F)c(N#C)c2C3=CC=C(C=C3)OCCCH3)c(C)c1</chem>	B1	A1	III	B	II	B
176	 <chem>N#Cc1cc(C(F)(F)F)c(NCc2ccccc2)c(c1)C3=CC=C(C=C3)OCC4=CC=CC=C4</chem>	C1	B1	II	A	III	B
177	 <chem>Cc1ccc(CCNc2cc(C(F)(F)F)c(N#C)c2C3=CC=C(C=C3)OCC4=CC=CC=C4)cc1</chem>	B1	B1	III	B	III	B

FIG. 1AI

(36/78)

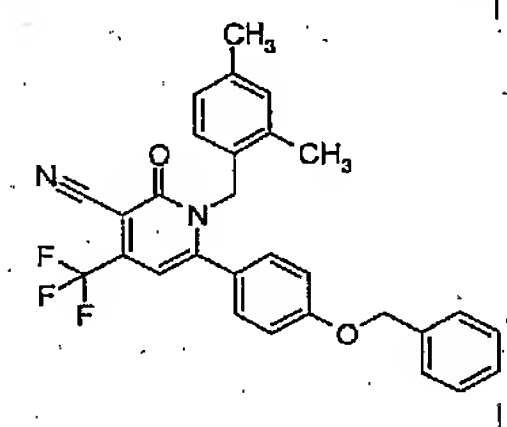
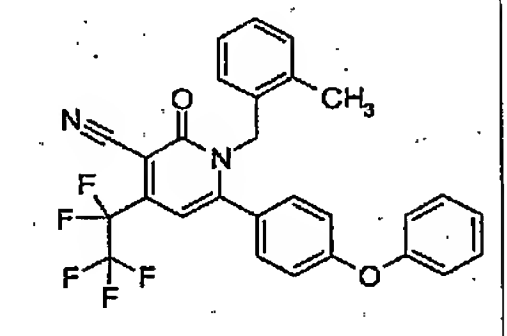
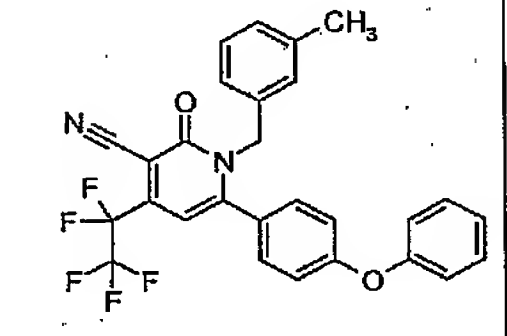
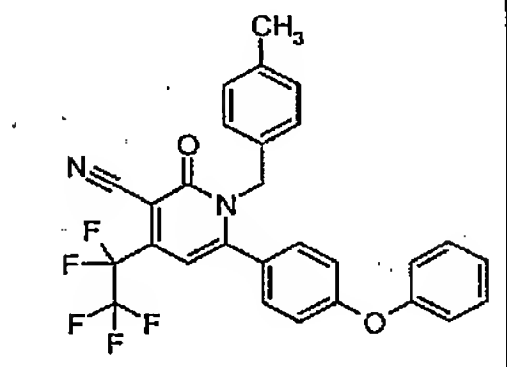
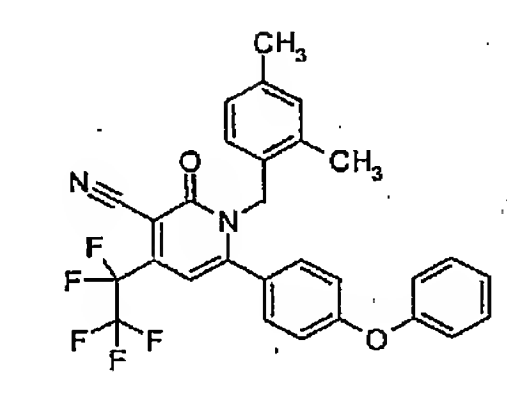
178		B1	A1	III	B	III	B
179		A1	A1	II	B	III	C
180		A1	A1	II	C	IV	C
181		A1	A1	II	B	II	C
182		A1	A1	II	B	II	C

FIG. 1AJ

(37/78)

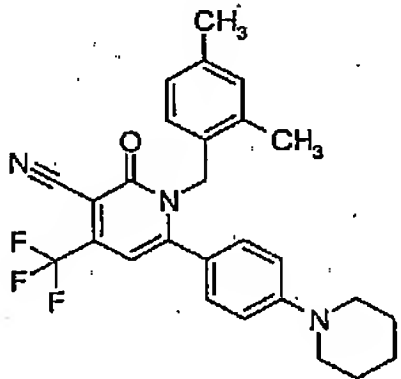
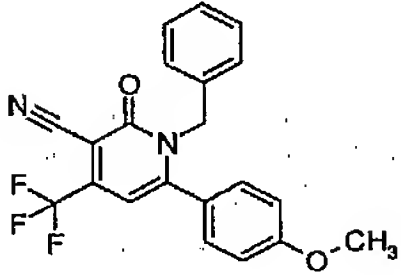
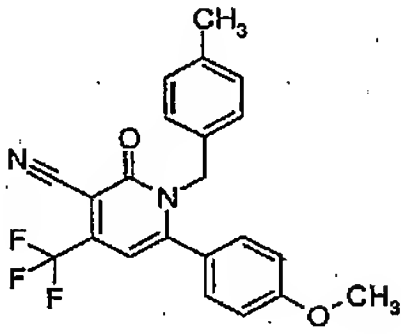
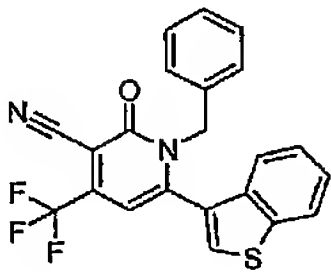
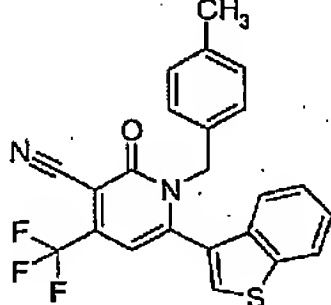
183-1		A1	A1	II	B	II	C
183-2		A1	A1	II	B	II	C
184		C1	B1	IV	B	IV	C
185		B1	A1	III	B	III	C
186		C1	B1	III	B	III	B
187		B1	A1	III	B	III	C

FIG. 1AK

(38/78)

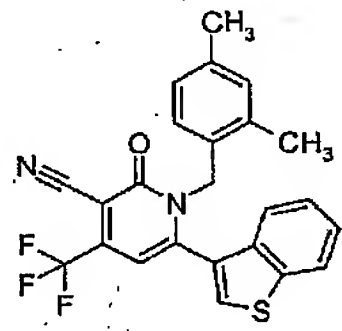
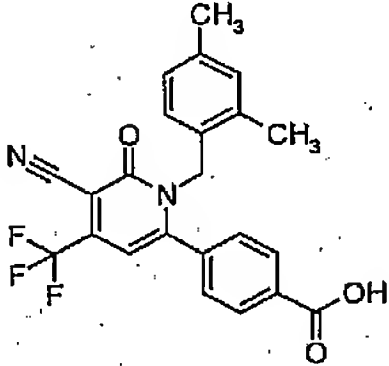
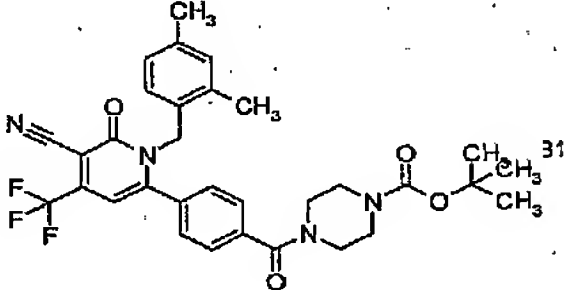
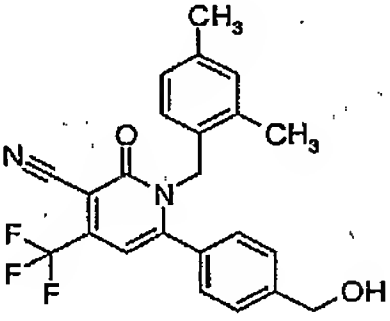
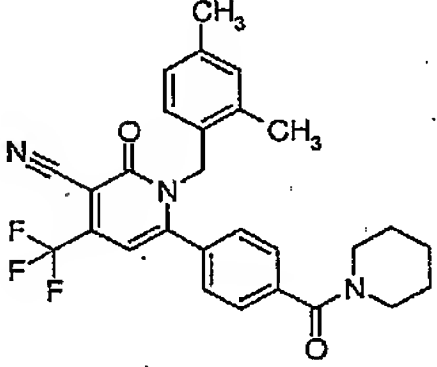
188		B1	A1	III	B	III	C
189		D1	D1	NC	B	NC	NC
190		B1		III	B	IV	D
191		B1	A1	III	B	III	C
192		B1	B1	III	B	IV	D

FIG. 1AL

(39/78)

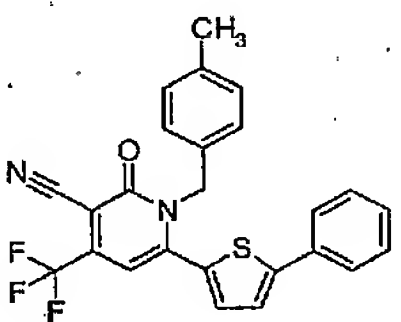
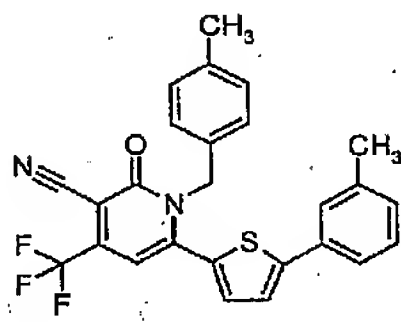
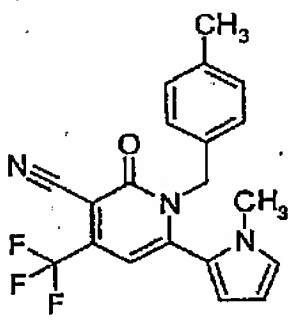
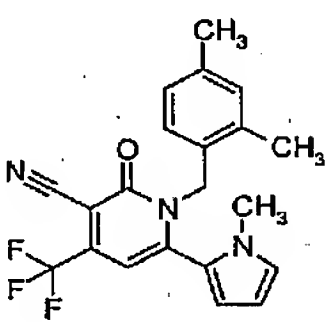
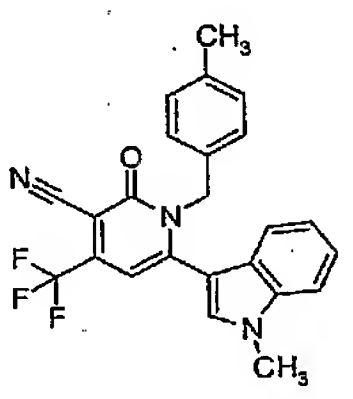
193		C1	B1	III	B	III	C
194		C1	B1	III	B	III	C
195		B1	B1	III	B	III	C
196		B1	A1	III	C	III	D
197		D1	B1	III	B	III	C

FIG. 1AM

(40/78)

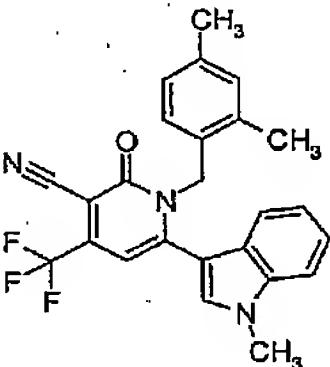
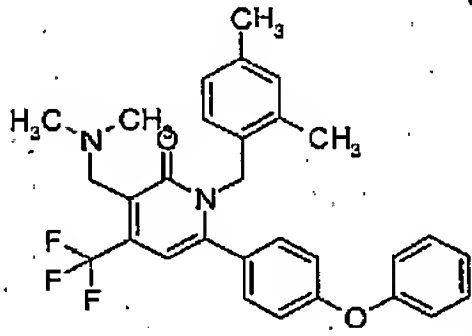
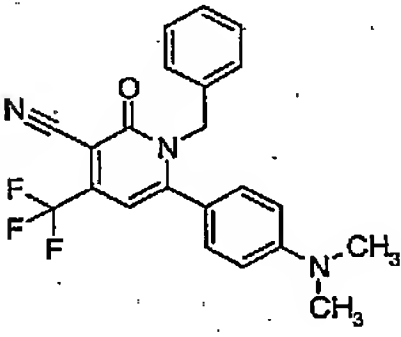
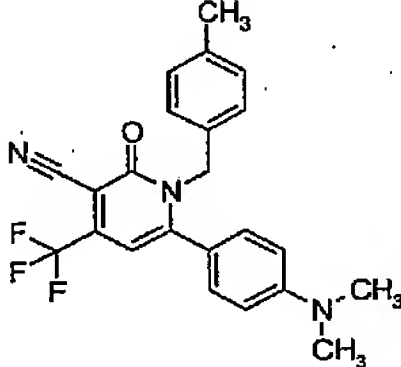
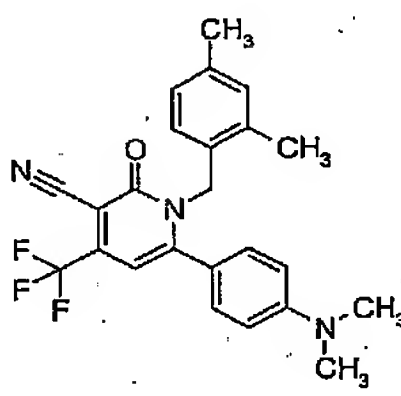
198		D1	D1	IV	B	IV	B
199		A1	A1	III	B	III	C
200		D1	C1	IV	A	III	A
201		B1	B1	III	B	III	B
202		B1	A1	III	B	III	C

FIG. 1AN

(41/78)

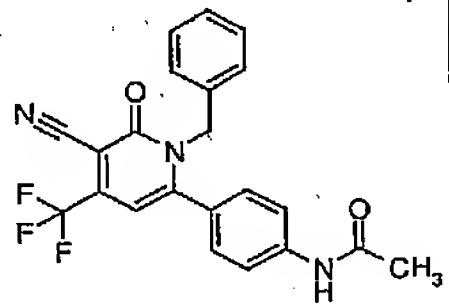
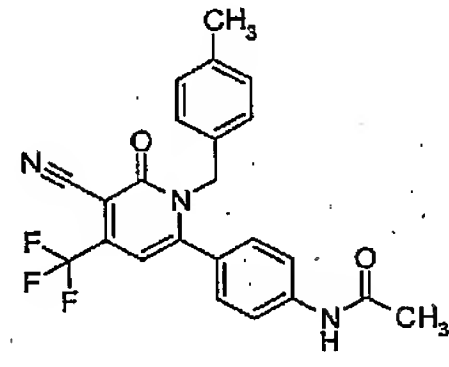
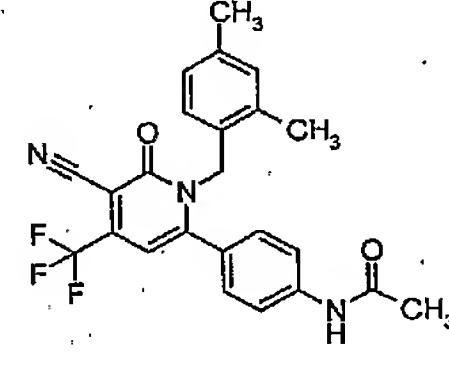
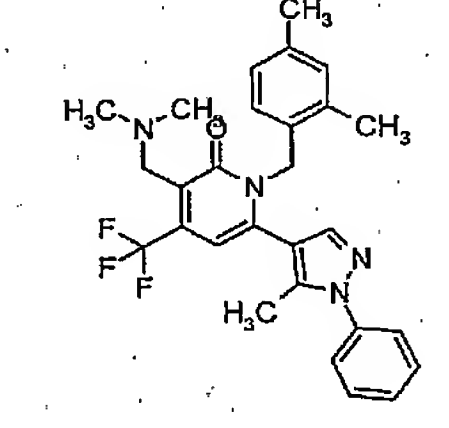
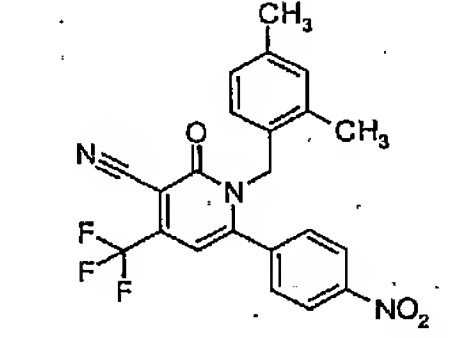
203		D1	D1	IV	A	NC	NC
204		D1	D1	IV	B	IV	B
205		C1	C1	III	B	IV	B
206		C1	B1	IV	C	NC	D
207		C1	B1	IV	B	IV	C

FIG. 1AO

(42/78)

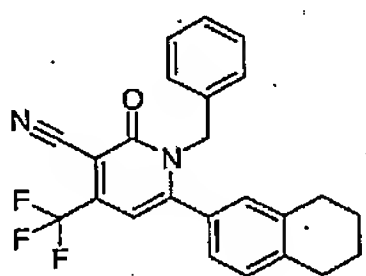
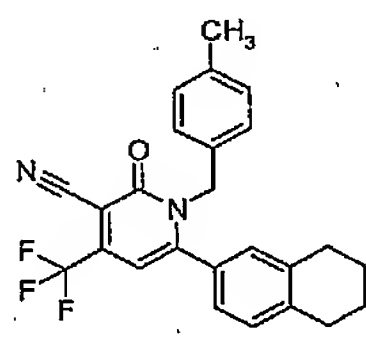
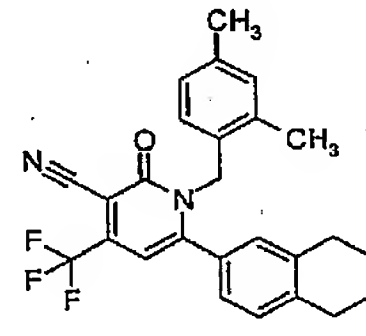
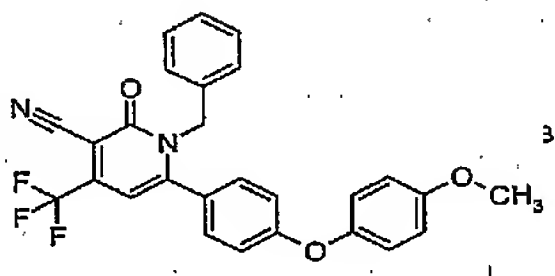
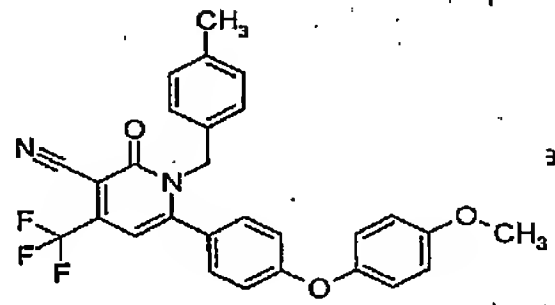
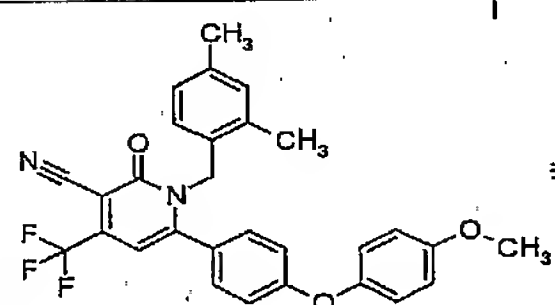
208		B1	B1	III	A	III	B
209		B1	A1	III	B	III	C
210		B1	B1	III	B	III	C
211		31	B1	III	C	III	C
212		31	A1	III	C	III	C
213		31	A1	II	C	II	D

FIG. 1AP

(43/78)

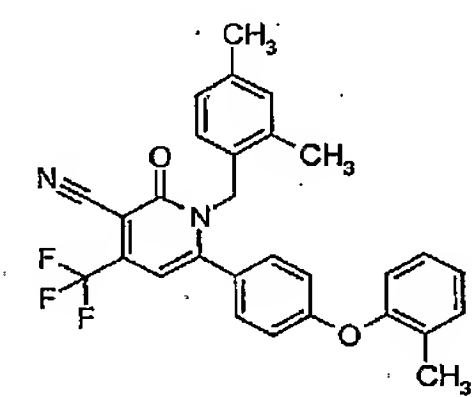
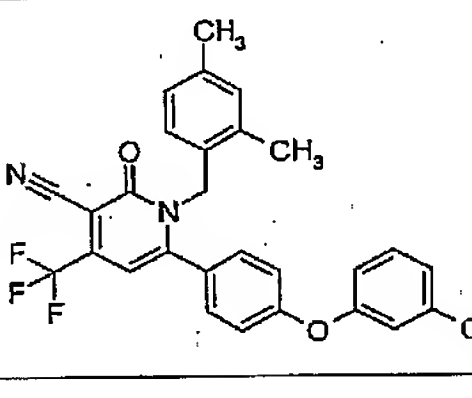
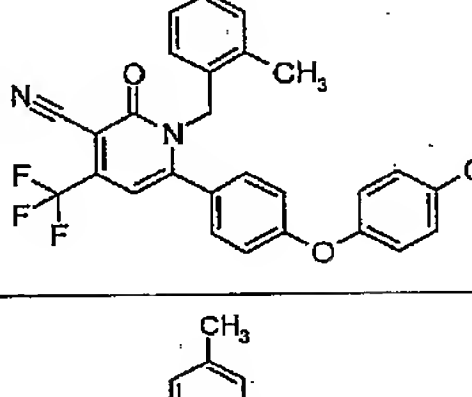
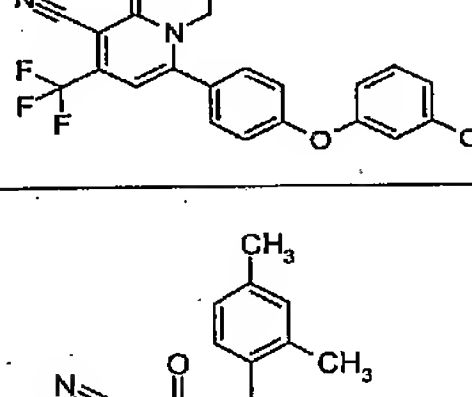
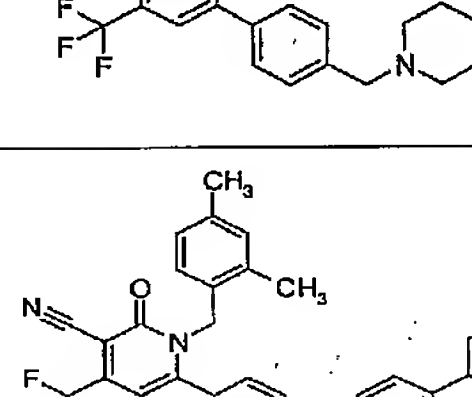
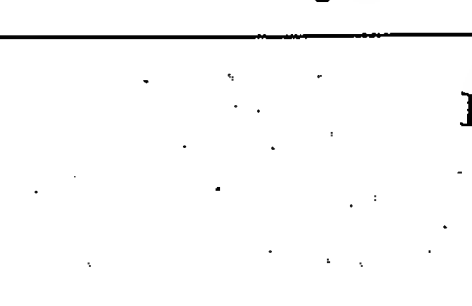
214		A1	A1	II	B	II	C
215		A1	A1	II	C	II	D
216		A1	A1	III	C	II	C
217		A1	A1	II	C	II	C
218		B1	B1	IV	B	IV	B
219		B1	B1	II	B	II	B

FIG. 1AQ

(44/78)

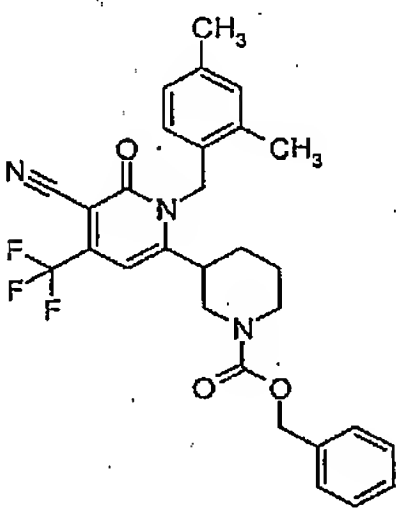
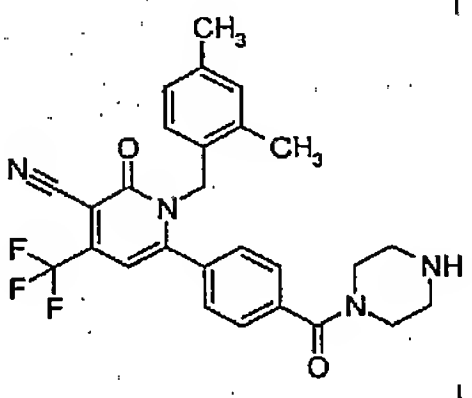
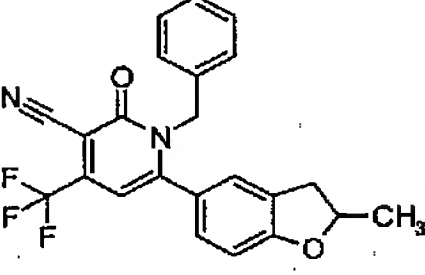
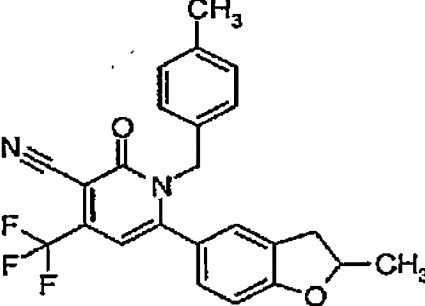
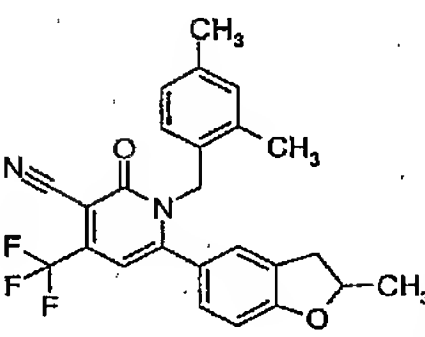
220		B1	A1	III	B	III	B
221		D1	D1	NC	B	IV	B
222		C1	B1	III	A	NC	C
223		B1	A1	III	B	III	B
224		A1	A1	III	B	III	B

FIG. 1AR

(45/78)

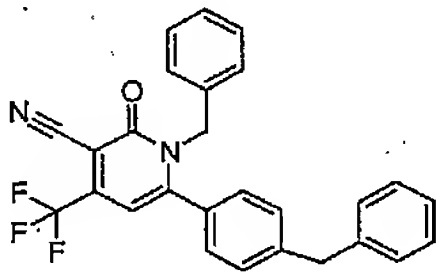
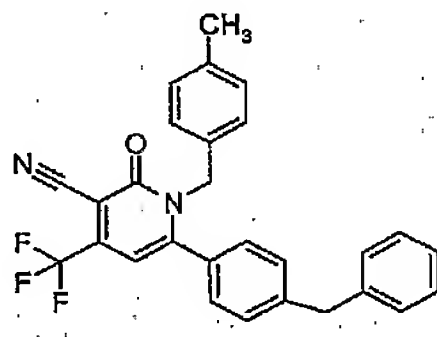
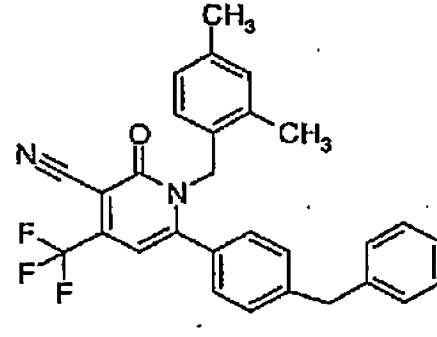
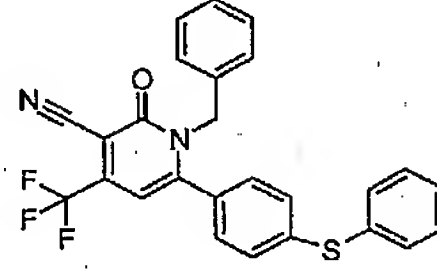
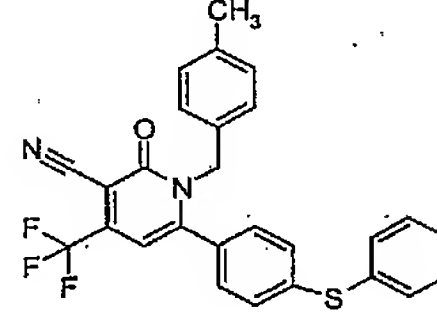
225		D1	B1	IV	A	III	B
226		B1	B1	III	B	III	B
227		B1	A1	III	B	III	B
228		C1	B1	IV	B	III	B
229		B1	B1	III	B	III	C

FIG. 1AS

(46/78)

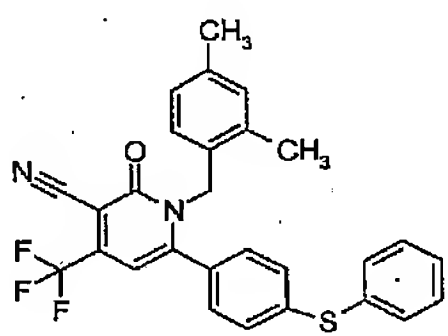
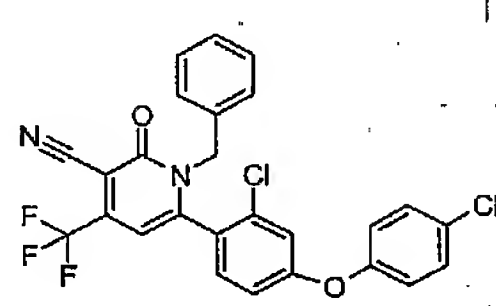
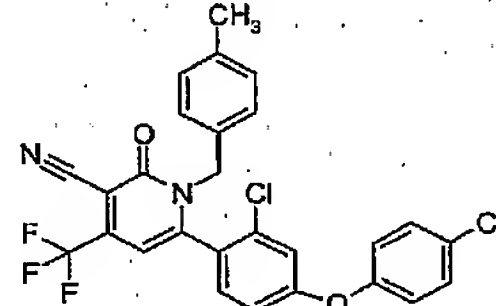
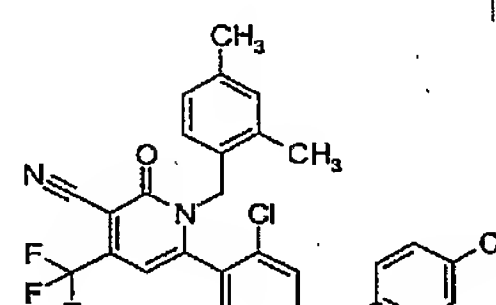
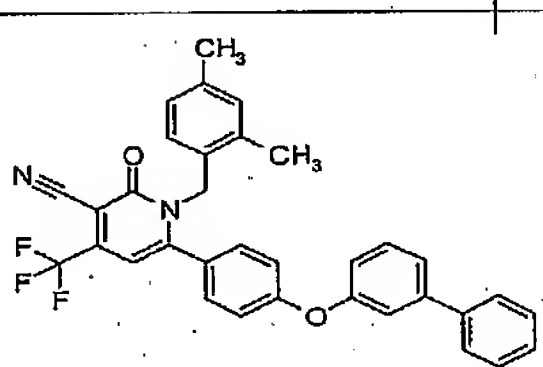
230		B1	A1	III	B	III	C
231		B1	B1	III	B	III	C
232		A1	A1	III	B	III	C
233		B1	A1	II	B	II	C
234		31	A1	III	B	NC	C

FIG. 1AT

(47/78)

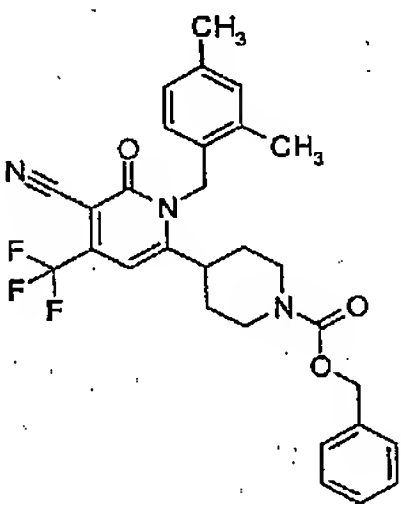
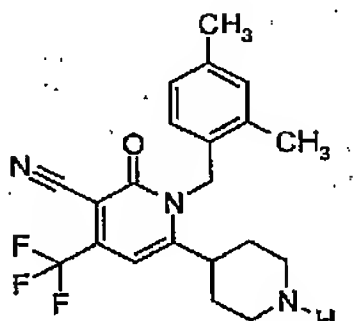
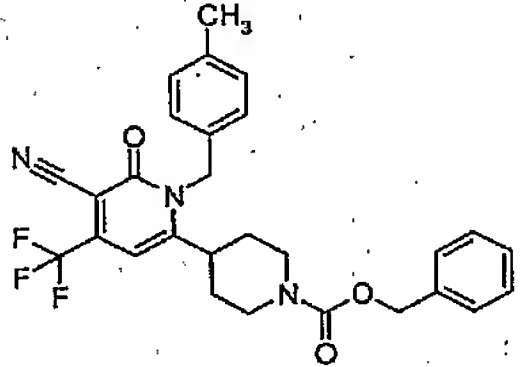
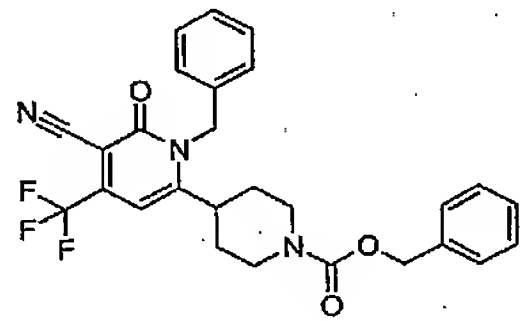
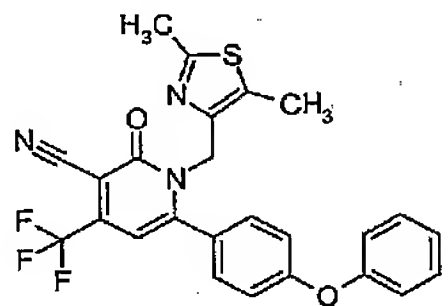
235		D1	D1	IV	A	NC	A
236		NC	NC	NC	NC	NC	NC
237-1		D1	D1	IV	A	IV	B
237-2		D1	C1	IV	A	IV	B
238		NC	NC	NC	A	NC	B
239		B1	B1	III	B	III	B

FIG. 1AU

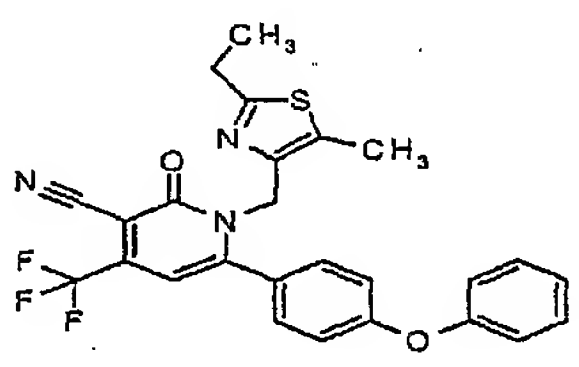
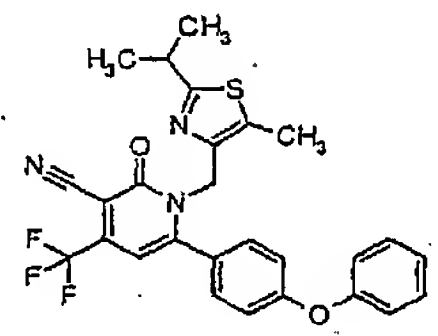
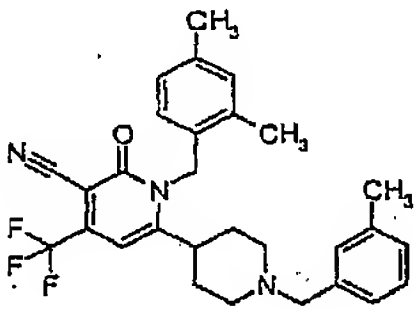
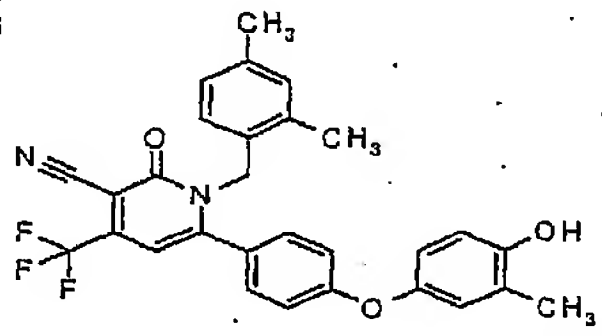
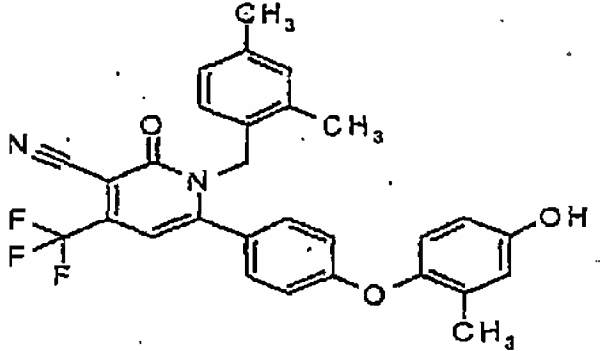
240		B1	B1	III	B	III	C
241		D1	C1	III	B	IV	B
242		B1	B1	NC	B	III	B
243		A1	A1	II	B	II	C
244		A1	A1	I	B	I	C

FIG. 1AV

(49/78)

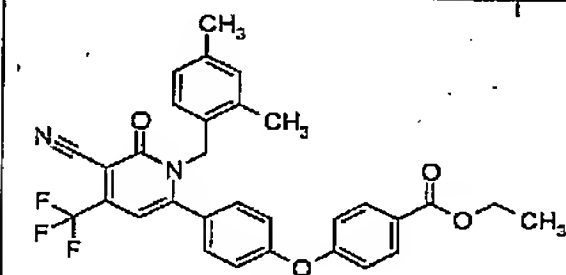
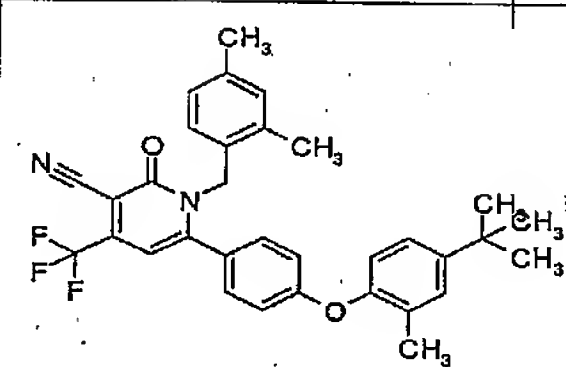
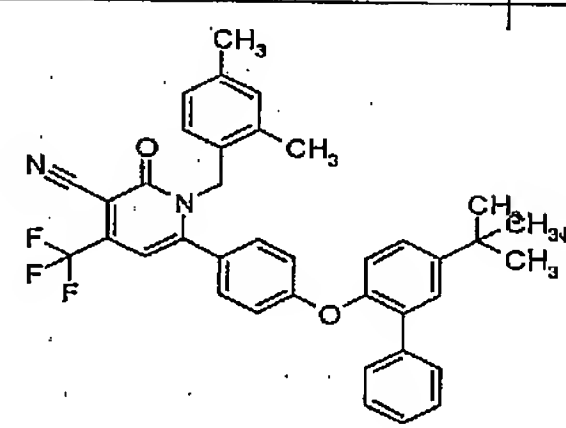
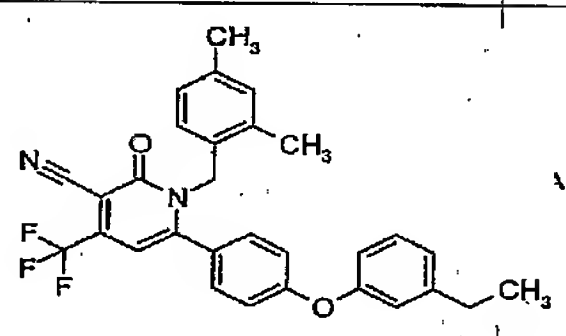
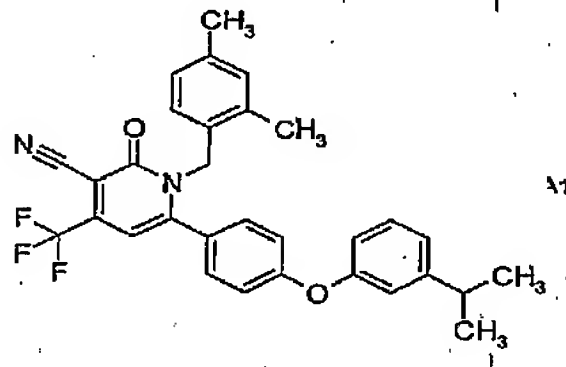
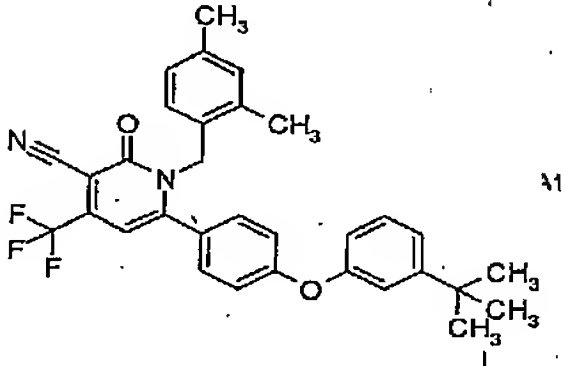
245		A1	II	B	II	C
246		A1	III	B	III	C
247		NC	NC	NC	IV	A
248		A1	I	B	II	C
249		A1	II	C	II	C
250		A1	II	C	II	C

FIG. AW

(50/78)

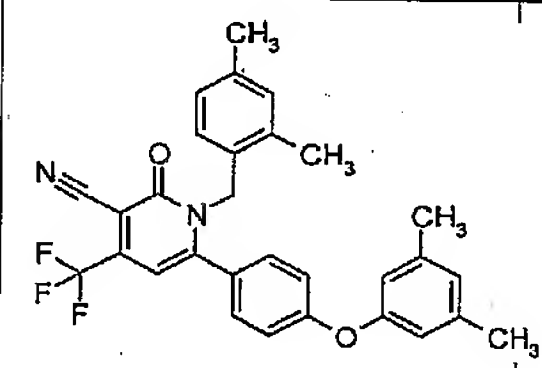
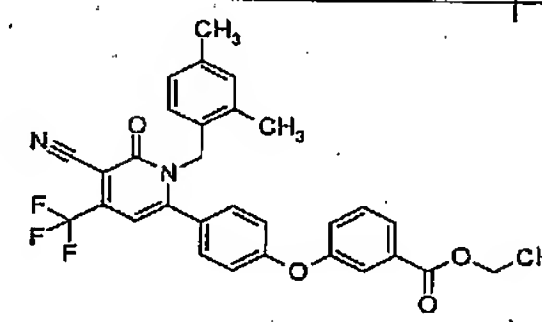
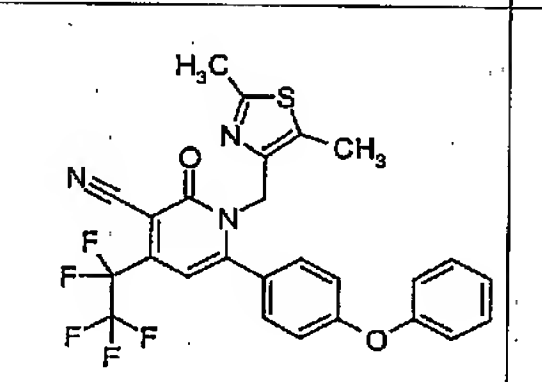
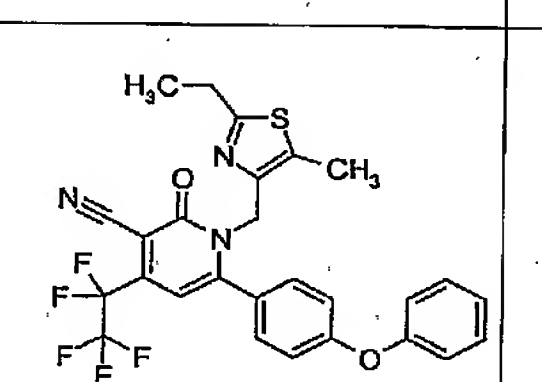
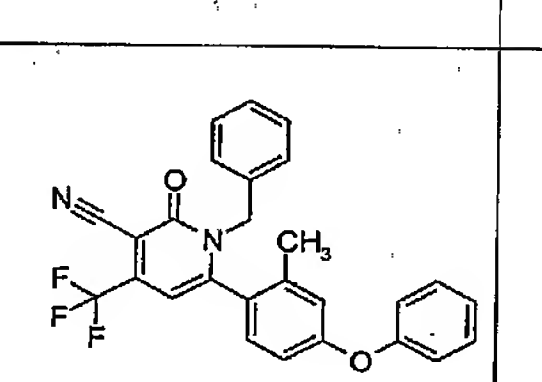
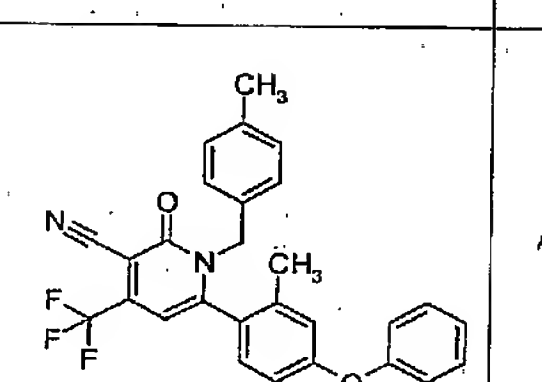
251		A1	A1	I	C	I	D
252		A1	A1	II	B	II	C
253		B1	B1	III	B	III	C
254		B1	B1	III	B	III	C
255		B1	A1	II	B	II	B
256		A1	A1	II	B	II	D

FIG. AX

(51/78)

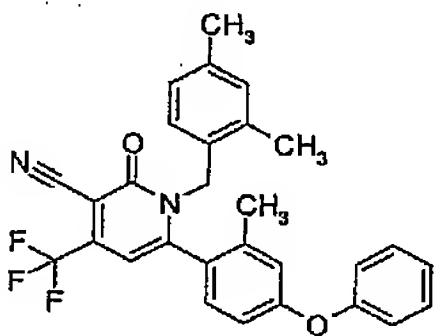
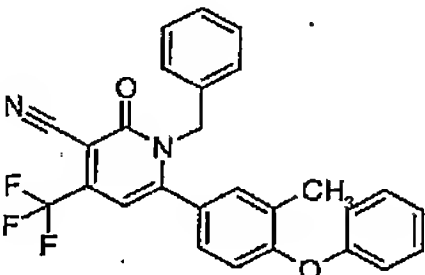
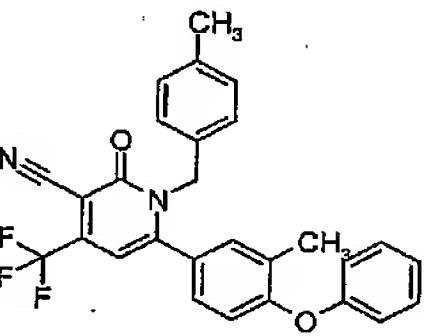
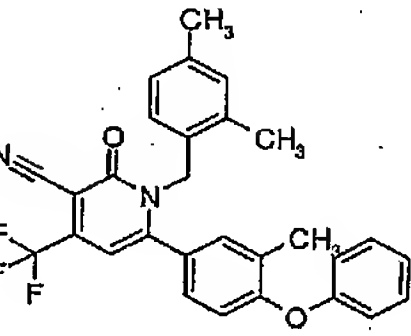
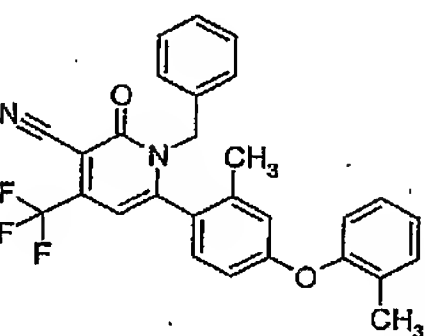
257		A1	A1	II	B	II	C
258		B1	B1	III	B	III	C
259		A1	A1	II	B	II	C
260		A1	A1	II	C	II	C
261		A1	A1	II	C	II	C

FIG. AY

(52/78)

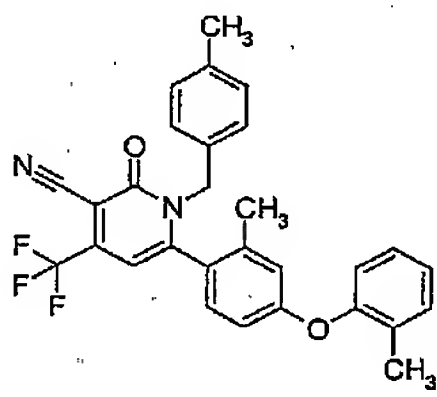
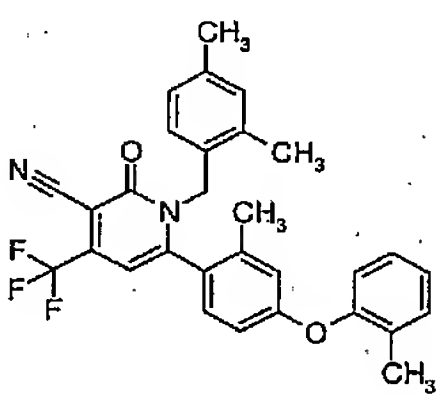
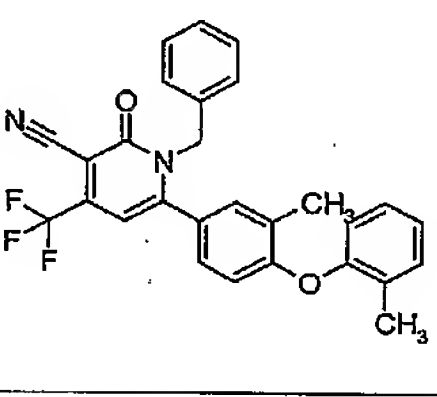
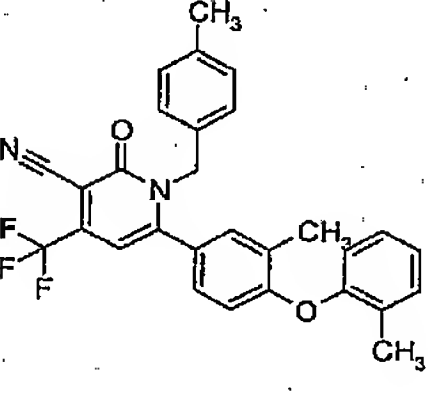
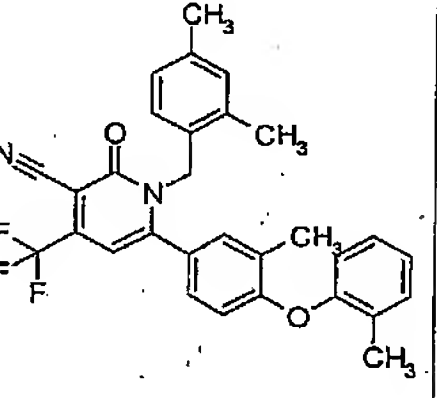
262		A1	A1	II	B	II	C
263		B1	A1	II	B	II	C
264		A1	A1	II	B	II	B
265		B1	A1	II	B	II	B
266		A1	A1	II	B	II	B

FIG. AZ

(53/78)

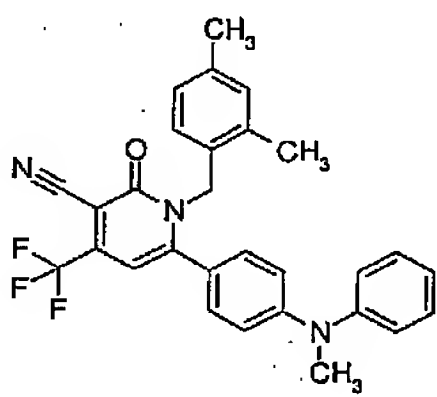
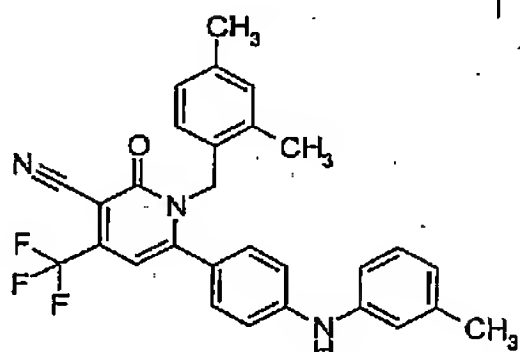
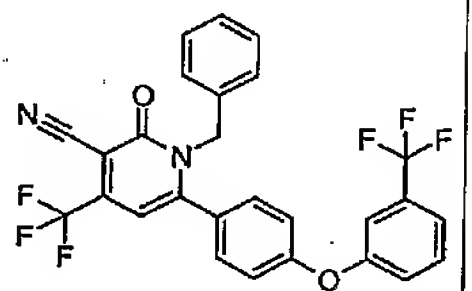
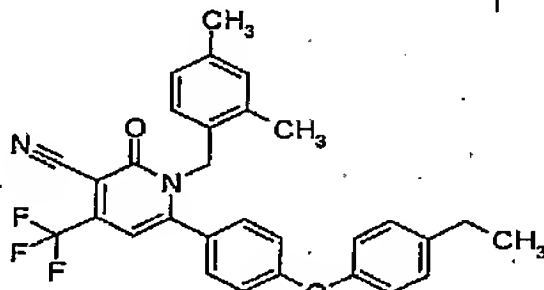
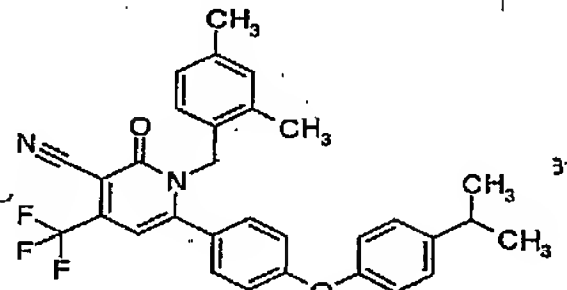
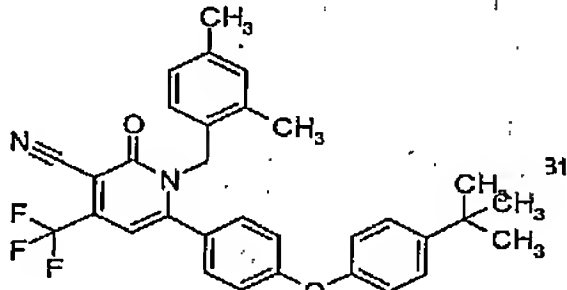
257		B1	A1	III	B	III	B
268		A1	A1	II	C	II	C
269		B1	A1	III	B	II	C
270		A1	A1	II	C	II	C
271		A1	II	C	II	C	
272		B1	III	B	III	C	

FIG. 1BA

(54/78)

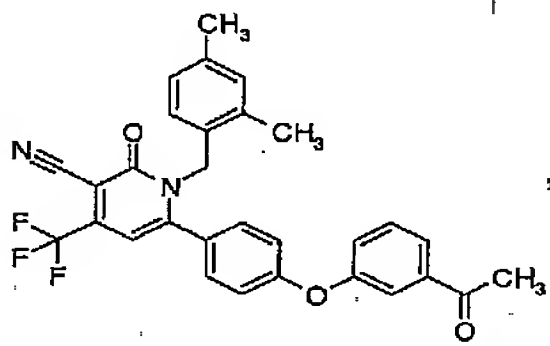
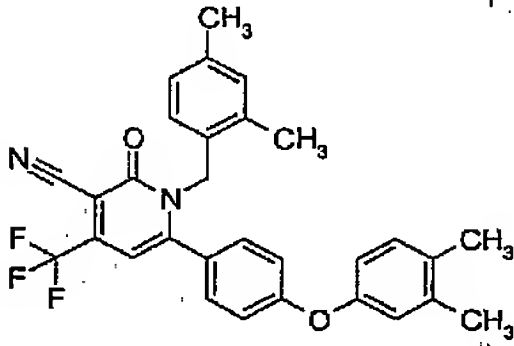
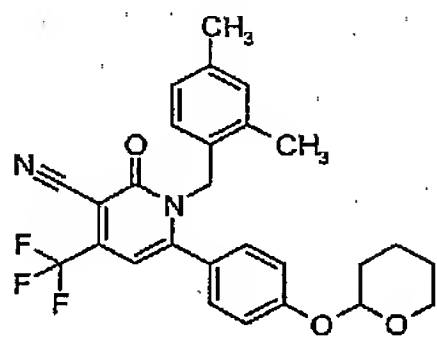
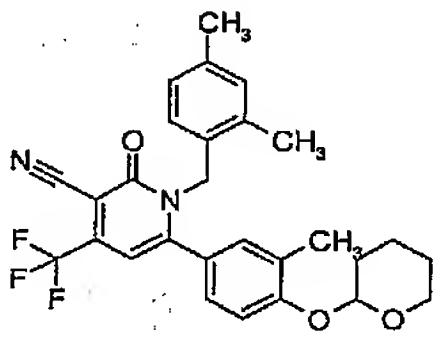
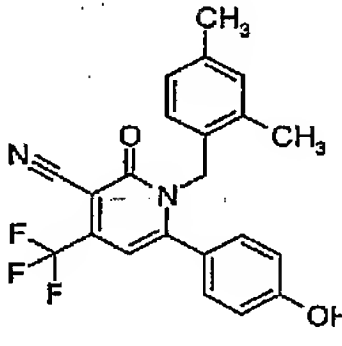
273		A1	A1	II	B	II	C
274		A1	A1	II	B	II	C
275		A1	B1	II	B	III	B
276		A1	A1	III	B	III	B
277		B1	A1	III	B	III	B

FIG. 1BB

(55/78)

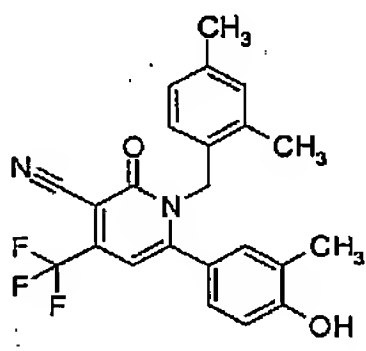
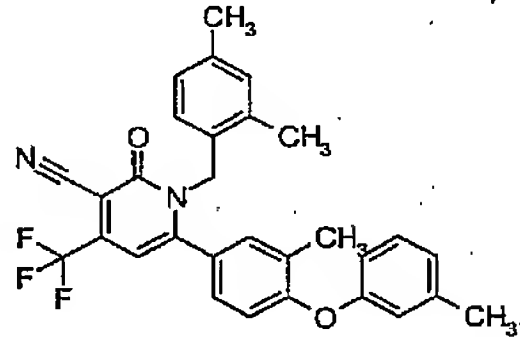
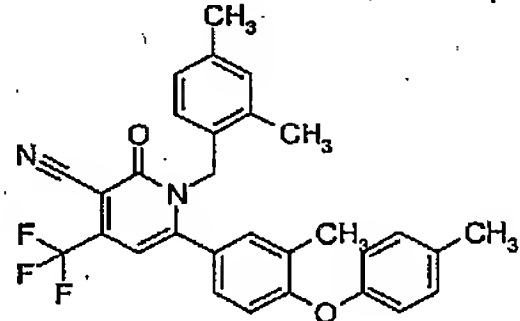
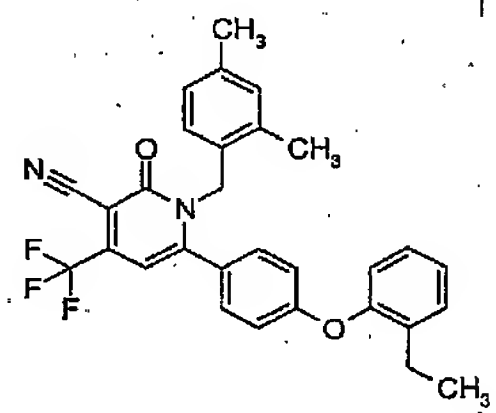
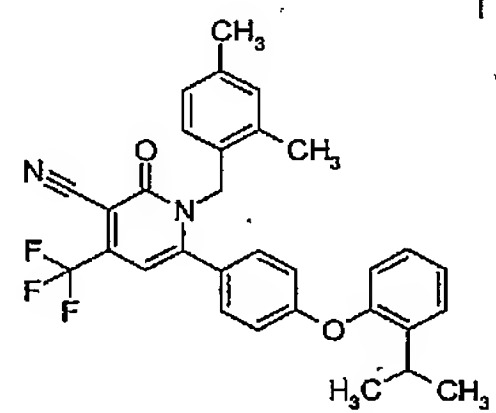
278		B1	B1	III	B	III	B
279		A1	A1	II	B	II	B
280		B1	B1	III	B	III	B
281		A1	A1	II	B	II	B
282		A1	A1	II	B	II	B

FIG. 1BC

(56/78)

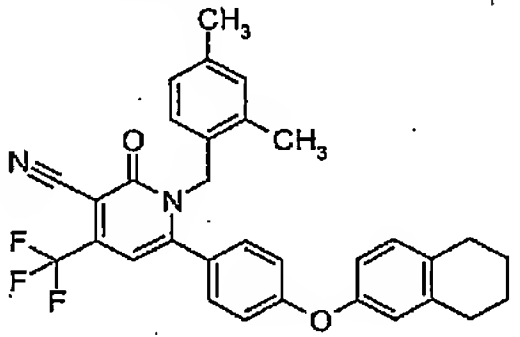
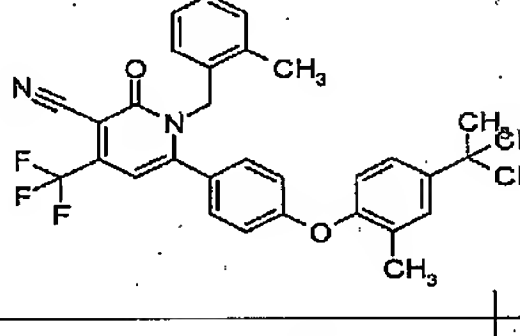
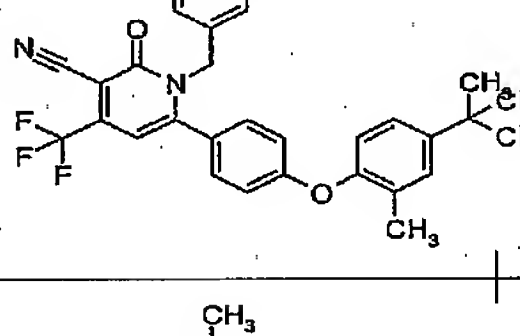
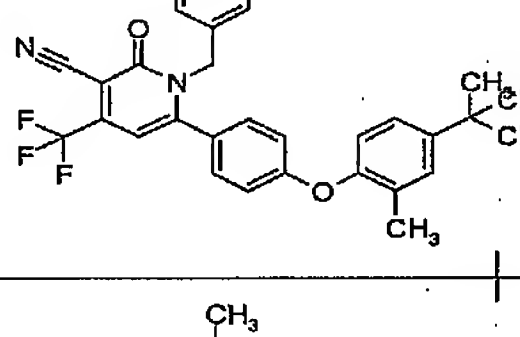
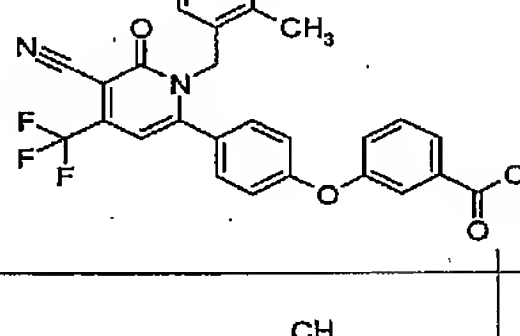
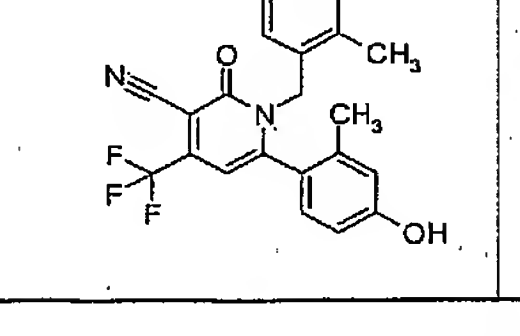
283	 <chem>Cc1cc(C)ccc1CN1C(=O)c2cc(C(F)(F)F)cc(C#N)c2C1c3ccc(Oc4ccc5c(c3)CCCC5)cc4</chem>	A1	A1	II	B	II	B
284	 <chem>Cc1cc(C)ccc1CN1C(=O)c2cc(C(F)(F)F)cc(C#N)c2C1c3ccc(Oc4ccc(C(C)C)cc4C(C)C)cc3</chem>	B1	B1	III	B	III	C
285	 <chem>Cc1cc(C)ccc1CN1C(=O)c2cc(C(F)(F)F)cc(C#N)c2C1c3ccc(Oc4ccc(C(C)C)cc4C(C)C)cc3</chem>	B1	B1	III	B	III	B
286	 <chem>Cc1cc(C)ccc1CN1C(=O)c2cc(C(F)(F)F)cc(C#N)c2C1c3ccc(Oc4ccc(C(C)C)cc4C(C)C)cc3</chem>	A1	A1	III	B	III	C
287	 <chem>Cc1cc(C)ccc1CN1C(=O)c2cc(C(F)(F)F)cc(C#N)c2C1c3ccc(Oc4ccc(C(=O)O)cc4)cc3</chem>	A1	A1	III	B	III	B
288	 <chem>Cc1cc(C)ccc1CN1C(=O)c2cc(C(F)(F)F)cc(C#N)c2C1c3ccc(O)cc3</chem>	A1	A1	III	B	III	B

FIG. 1BD

(57/78)

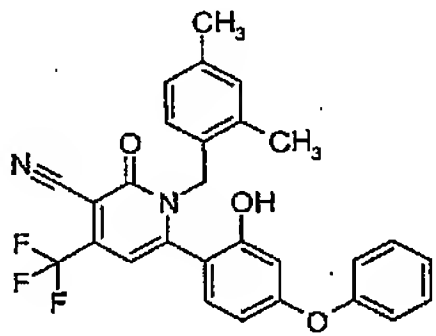
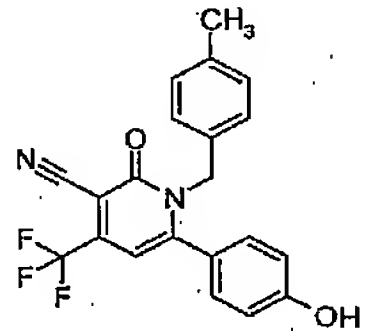
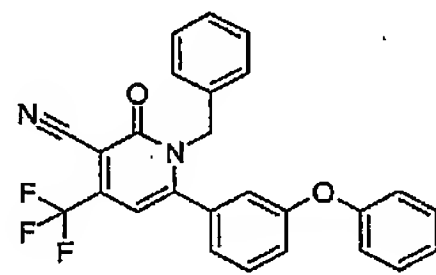
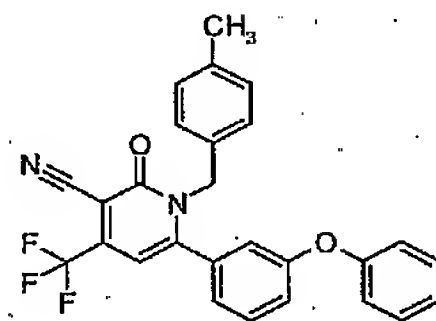
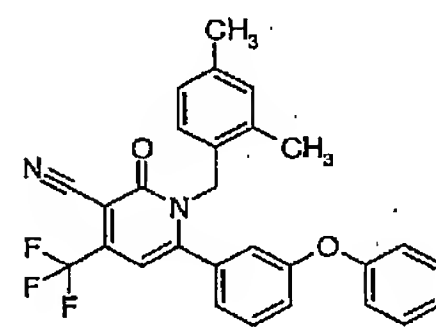
289		A1	B1	III	B	III	B
290		B1	B1	III	B	III	B
291		B1	A1	III	B	III	B
292		B1	A1	III	B	III	B
293		A1	A1	II	B	II	B

FIG. 1BE

(58/78)

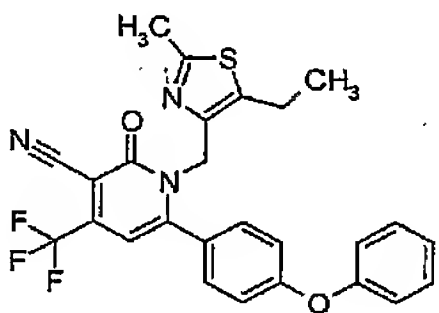
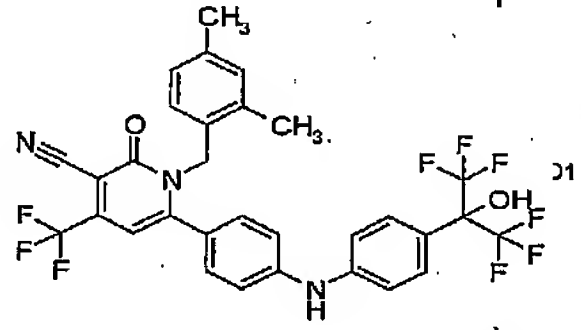
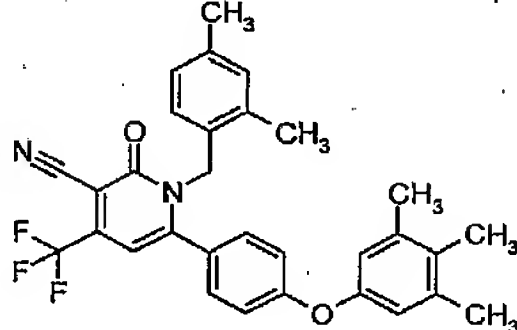
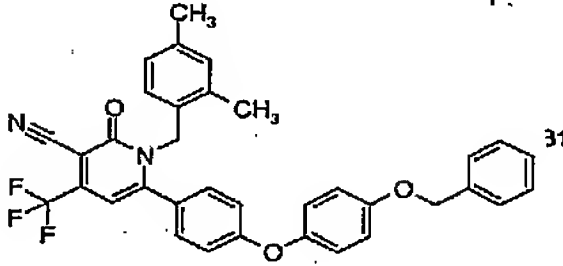
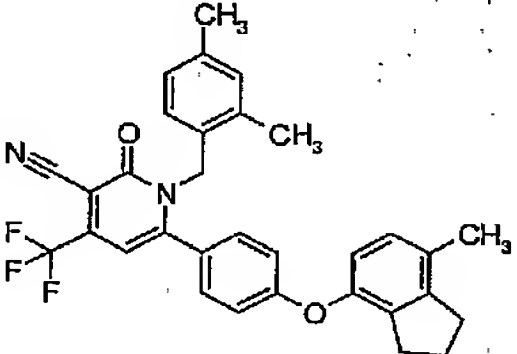
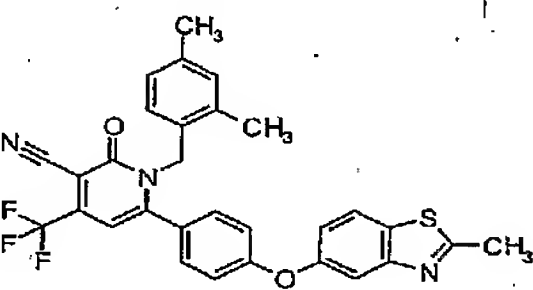
294		B1	B1	III	B	III	B
295		C1	II	B	II	B	
296		A1	A1	II	B	II	C
297		B1	II	C	II	C	
298		A1	A1	II	B	II	C
299		A1	B1	II	B	II	B

FIG. 1BF

(59/78)

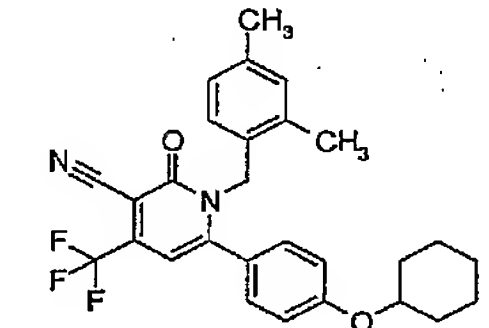
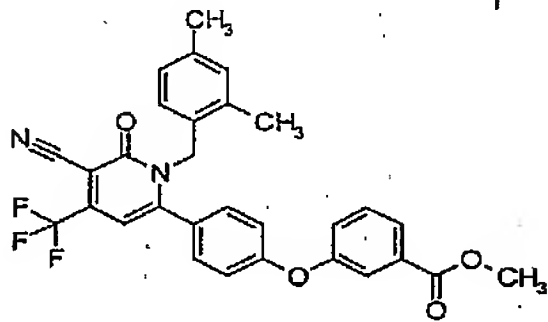
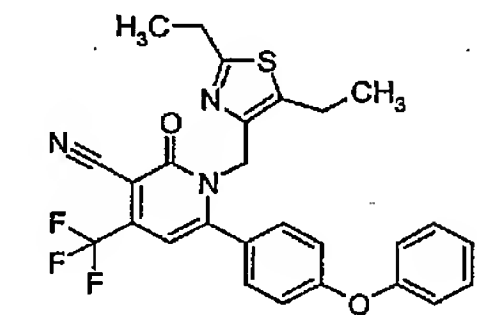
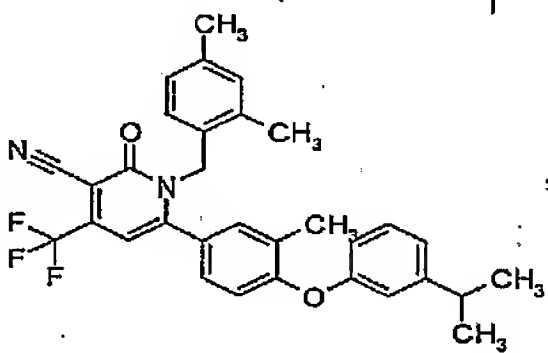
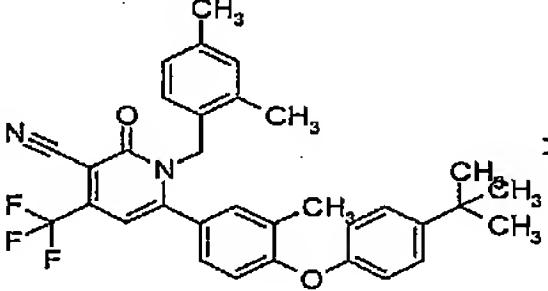
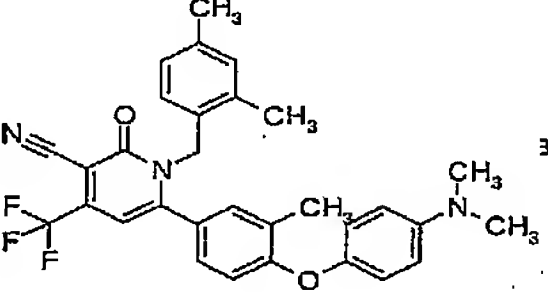
300		B1	B1	II	B	II	B
301		A1	A1	II	B	II	C
302		B1	B1	III	B	III	B
303		A1	A1	II	B	II	B
304		B1	B1	III	B	III	C
305		A1	A1	II	B	II	C

FIG. 1BG

(60/78)

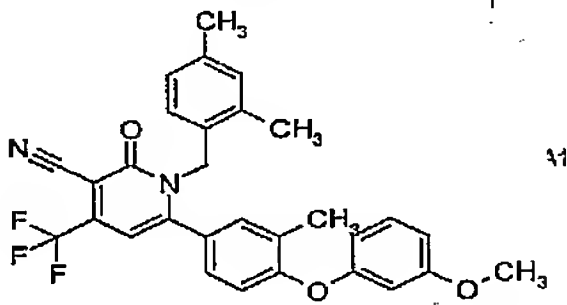
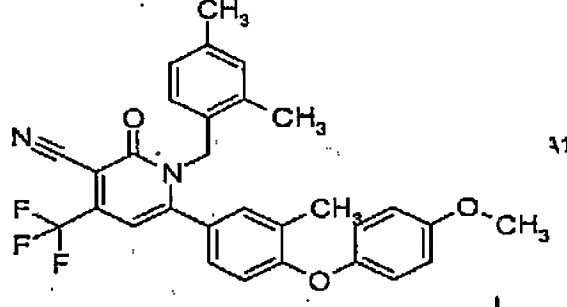
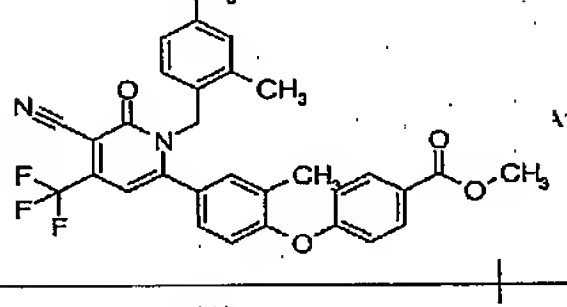
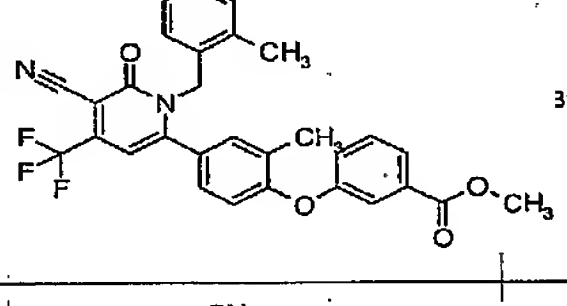
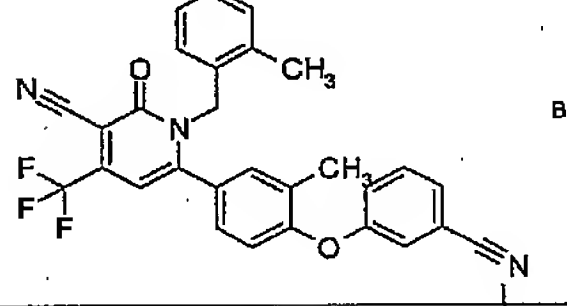
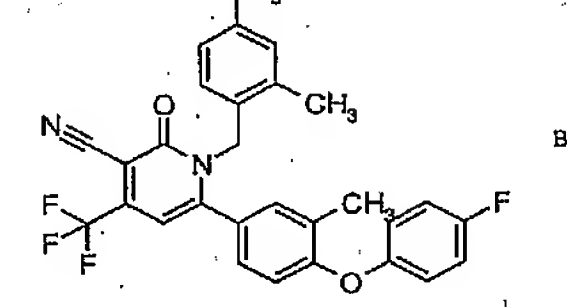
306	 A1	A1	II	B	II	C
307	 A1	A1	III	B	III	C
308	 A1	A1	III	B	III	C
309	 31	A1	III	B	III	C
310	 B1	B1	III	B	III	C
311	 B1	A1	III	B	II	C

FIG. 1BH

(61/78)

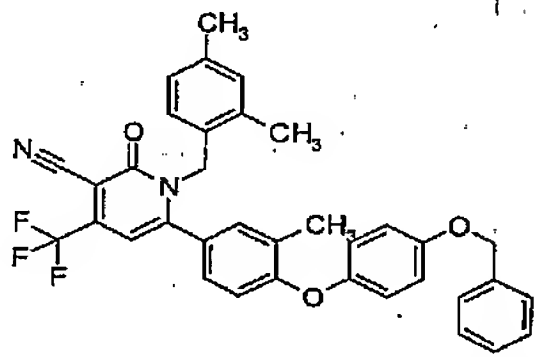
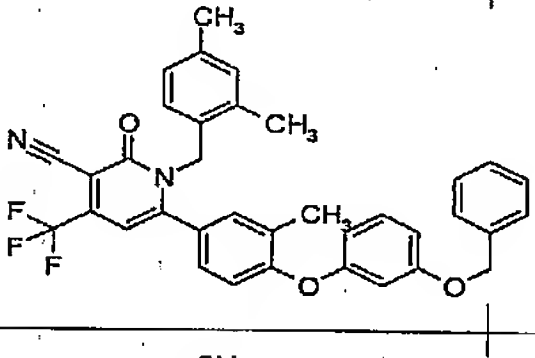
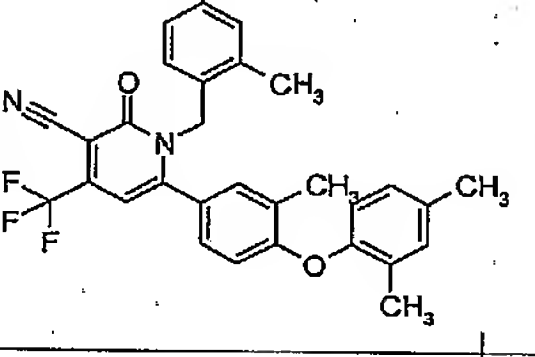
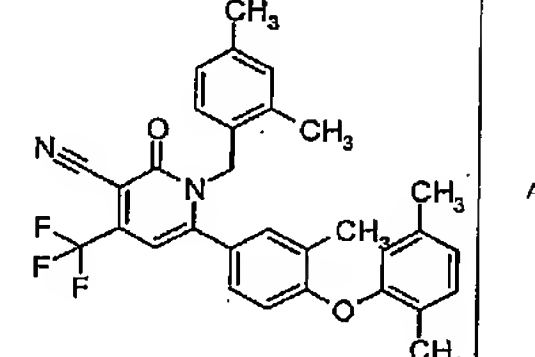
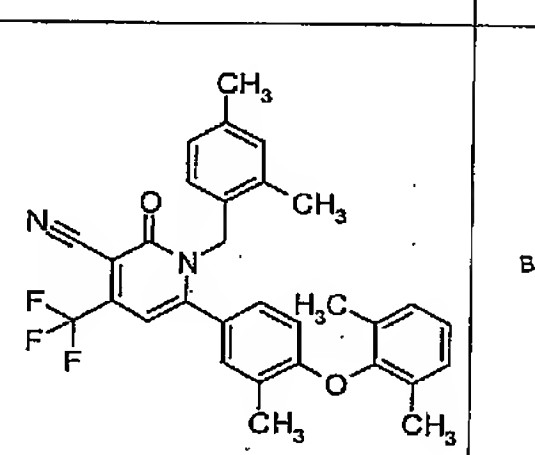
312	 31	C1	II	C	II	D
313	 31	C1	III	B	III	C
314	 B1	A1	III	B	II	C
315	 A1	A1	II	B	II	C
316	 B1	B1	III	B	III	B

FIG. 1BI

(62/78)

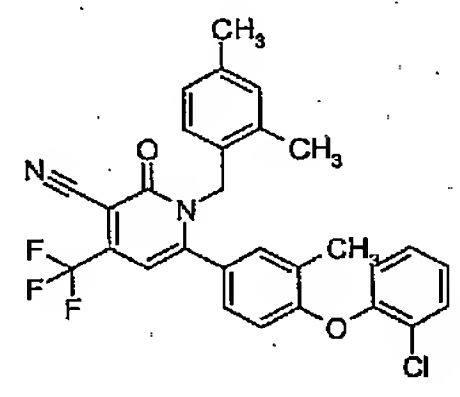
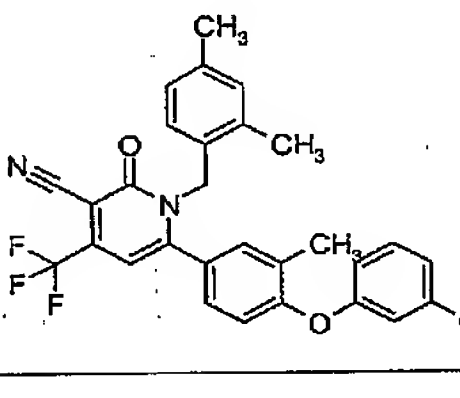
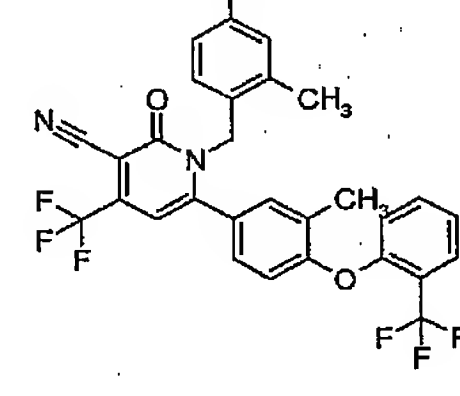
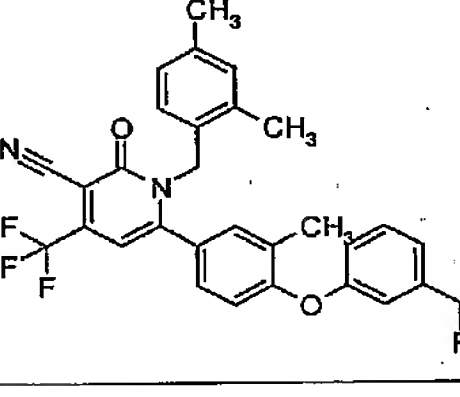
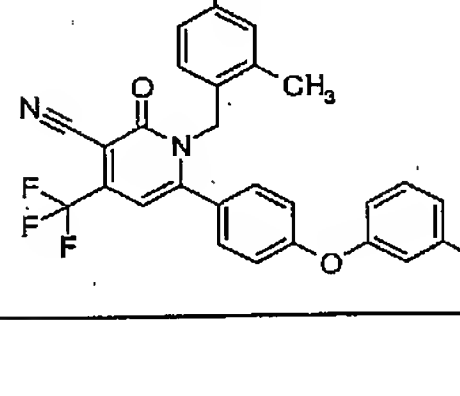
317		A1	A1	II	B	II'	C
318		A1	A1	II	B	II	C
319		A1	A1	II	B	II	C
320		A1	A1	II	B	II	C
321		A1	A1	II	B	II	D

FIG. 1BJ

(63/78)

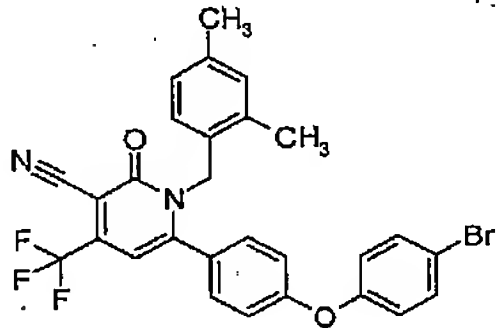
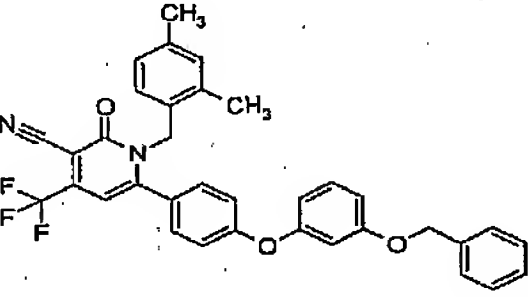
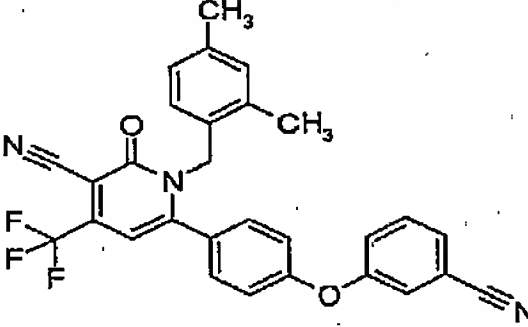
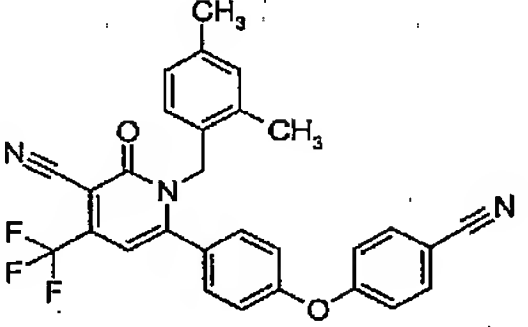
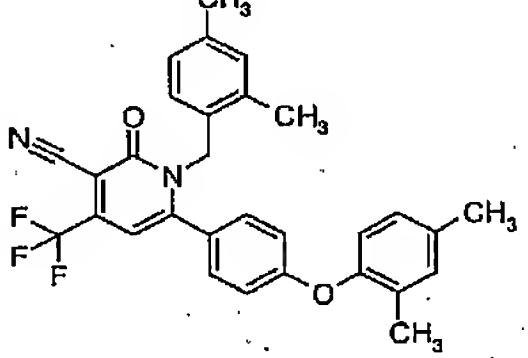
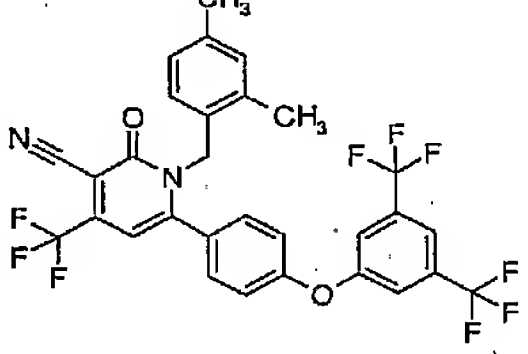
322	 A1	A1	III	B	III	C
323	 B1	B1	II	B	II	C
324	 A1	A1	II	B	II	D
325	 B1	B1	III	B	III	C
326	 A1	A1	II	B	II	C
327	 B1	A1	II	B	II	D

FIG. 1BK

(64/78)

328	<chem>Cc1ccc(C)cc1CN(C1=CC=C(C=C1)C2=CC=C(C=C2)OC3=CC=C(C=C3)S(=O)(=O)C)C4=CC=CC(=C4)C5=CC(=CC=C5)C#N</chem>	A1	A1	II	B	II	C
329	<chem>Cc1ccc(C)cc1CN(C1=CC=C(C=C1)C2=CC=C(C=C2)OC3=CC=C(C=C3)N(C)C)C4=CC=CC(=C4)C5=CC(=CC=C5)C#N</chem>	A1	A1	II	B	II	C
330	<chem>Cc1ccc(C)cc1CN(C1=CC=C(C=C1)C2=CC=C(C=C2)OC3=CC=C(C=C3)c4c[nH]c5ccccc45)C4=CC=CC(=C4)C5=CC(=CC=C5)C#N</chem>	A1	A1	I	C	I	D
331	<chem>CC(C)(C)C(=O)OCC1CCN(CC1)OC2=CC=C(C=C2)C3=CC=C(C=C3)C4=CC(=CC=C4)C#N</chem>	A1	A1	II	B	II	B
332	<chem>Oc1ccc(OCC2=CC=C(C=C2)C3=CC=C(C=C3)C4=CC(=CC=C4)C#N)cc1</chem>	B1	A1	II	C	II	C
333	<chem>Cc1ccc(C)cc1CN(C1=CC=C(C=C1)C2=CC=C(C=C2)OC3=CC=C(C=C3)c4c[nH]c5ccccc45)C4=CC=CC(=C4)C5=CC(=CC=C5)C#N</chem>	A1	A1	II	B	II	C

FIG. 1BL

(65/78)

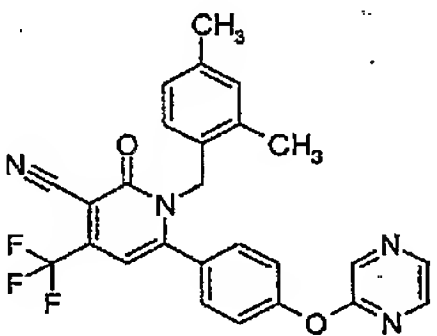
334		A1	A1	II	C	II	C
-----	--	----	----	----	---	----	---

FIG. 1BM

(66/78)

335		B1	B1	IV	B	IV	NC
336		D1	D1	NC	A	NC	NC
337		NC	NC	NC	A	NC	NC
338		NC	NC	NC	A	NC	NC
339		NC	NC	NC	A	NC	NC
340		NC	D1	NC	A	NC	NC
341		D1	D1	NC	A	NC	NC
342		NC	NC	NC	A	NC	NC
343		D1	D1	IV	B	NC	NC
344		D1	D1	IV	A	NC	NC
345		D1	D1	IV	A	NC	NC
346		NC	NC	NC	A	NC	NC
347		D1	B1	IV	B	NC	NC
348		D1	D1	IV	A	NC	NC

FIG. 1BN

(67/78)

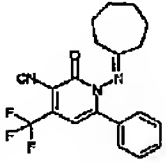
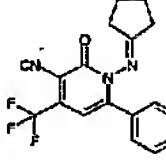
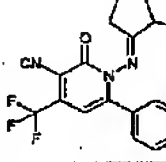
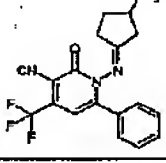
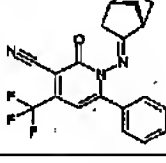
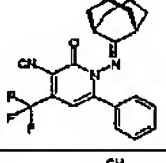
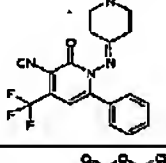
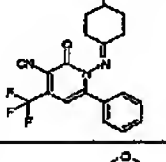
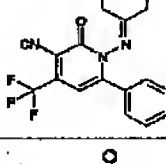
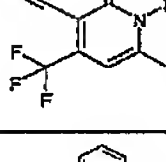
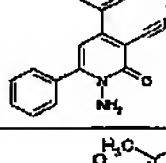
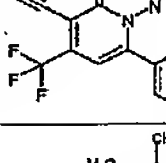
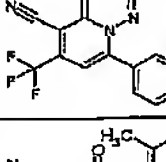
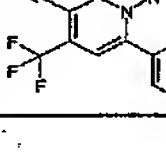
349		D1	B1	IV	B	NC	NC
350		D1	D1	NC	A	NC	NC
351		D1	C1	IV	B	NC	NC
352		D1	D1	IV	A	NC	NC
353		D1	D1	IV	B	NC	NC
354		D1	D1	NC	A	NC	NC
355		NC	D1	NC	A	NC	NC
356		NC	NC	NC	A	NC	NC
357		D1	D1	NC	A	NC	NC
358		NC	NC	NC	A	NC	NC
359		NC	NC	NC	A	NC	NC
360		D1	D1	IV	A	NC	NC
361		C1	B1	IV	B	NC	NC
362		D1	D1	NC	B	NC	NC

FIG. 1BO

(68/78)

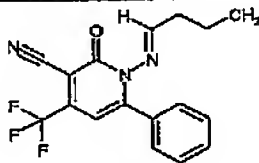
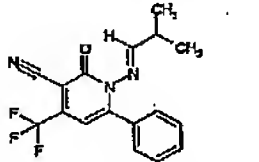
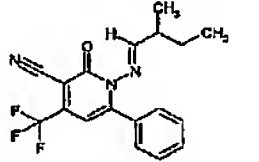
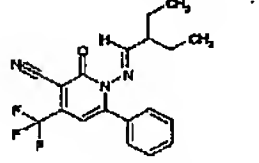
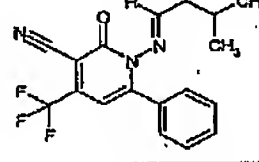
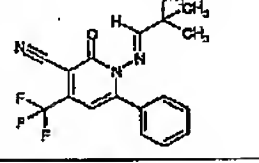
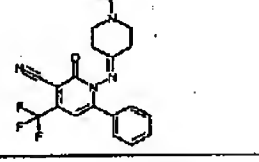
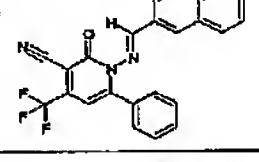
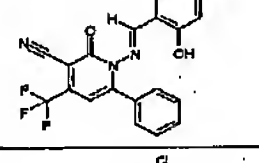
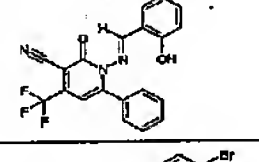
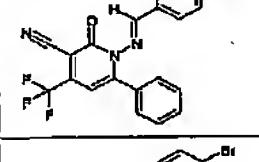
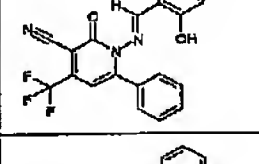
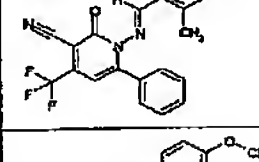
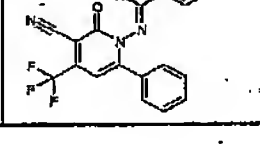
363		NC	D1	NC	A	NC	NC
364		D1	D1	NC	A	NC	NC
365		D1	D1	NC	A	NC	NC
366		NC	NC	NC	A	NC	NC
367		D1	D1	NC	A	NC	NC
368		NC	NC	NC	A	NC	NC
369		NC	NC	NC	A	NC	NC
370		NC	D1	NC	A	NC	NC
371		NC	D1	NC	A	NC	NC
372		NC	NC	NC	A	NC	NC
373		NC	D1	NC	A	NC	NC
374		NC	NC	NC	A	NC	NC
375		NC	NC	NC	A	NC	NC
376		NC	NC	NC	A	NC	NC

FIG. 1BP

(69/78)

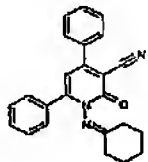
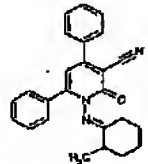
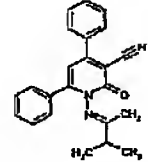
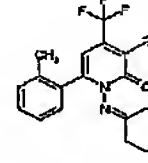
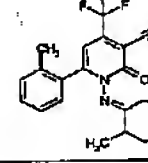
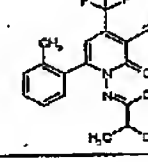
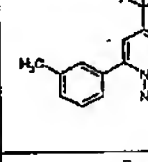
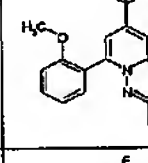
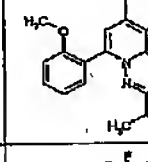
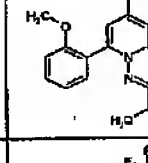
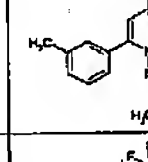
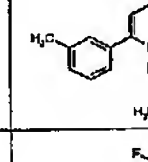
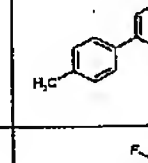
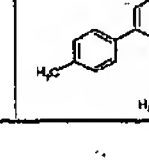
377		NC	NC	NC	A	NC	NC
378		NC	NC	NC	A	NC	NC
379		NC	NC	NC	A	NC	NC
380		C1	D1	IV	A	NC	NC
381		D1	C1	NC	A	NC	NC
382		D1	D1	IV	A	NC	NC
383		B1	B1	IV	B	NC	NC
384		C1	D1	IV	A	NC	NC
385		D1	D1	NC	A	NC	NC
386		D1	D1	IV	A	NC	NC
387		B1	B1	IV	A	NC	NC
388		B1	B1	IV	B	NC	NC
389		B1	B1	IV	B	NC	NC
390		C1	B1	IV	A	NC	NC

FIG. 1BQ

(70/78)

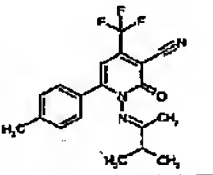
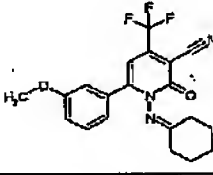
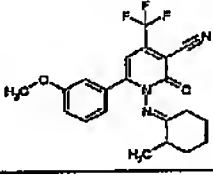
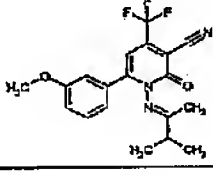
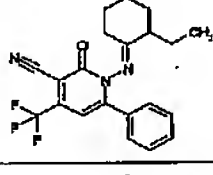
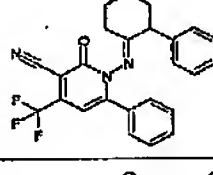
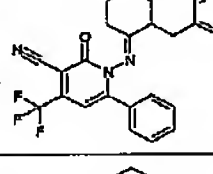
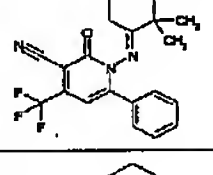
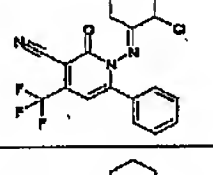
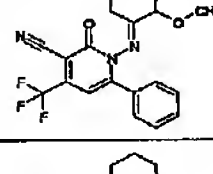
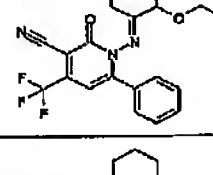
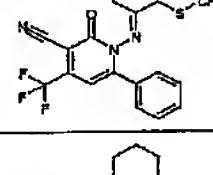
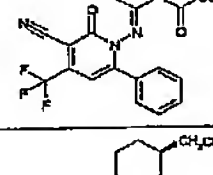
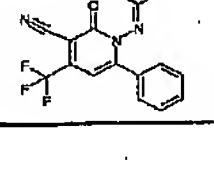
391		C1	C1	IV	A	NC	NC
392		B1	B1	IV	B	NC	NC
393		D1	B1	IV	B	III	B
394		C1	B1	IV	B	NC	NC
395		D1	D1	IV	A	NC	NC
396		NC	NC	NC	A	NC	NC
397		NC	NC	NC	A	NC	NC
398		D1	C1	IV	A	IV	NC
399		C1	B1	III	B	IV	NC
400		NC	NC	NC	A	NC	A
401		NC	NC	NC	A	NC	NC
402		NC	D1	IV	A	NC	NC
403		NC	NC	NC	A	NC	NC
404		NC	D1	IV	A	NC	NC

FIG. 1BR

(71/78)

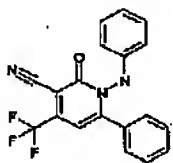
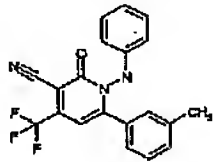
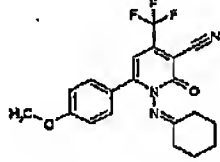
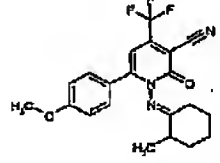
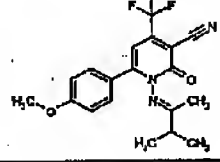
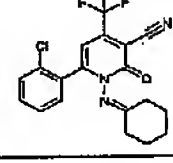
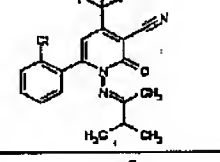
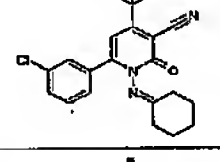
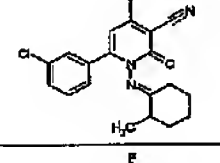
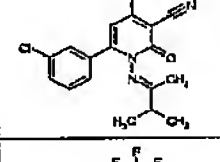
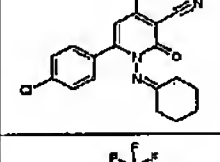
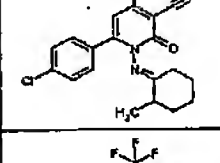
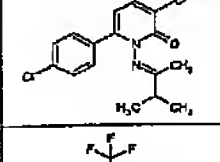
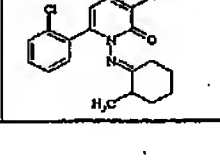
405		NC	D1	NC	A	NC	NC
406		NC	D1	IV	A	NC	NC
407		D1	C1	IV	C	IV	NC
408		D1	C1	IV	B	IV	NC
409		D1	D1	IV	B	IV	NC
410		B1	B1	III	B	IV	NC
411		B1	B1	III	B	IV	NC
412		C1	B1	III	B	IV	NC
413		C1	B1	III	A	IV	NC
414		C1	B1	IV	B	IV	NC
415		C1	C1	IV	B	IV	NC
416		NC	D1	IV	A	IV	NC
417		D1	D1	IV	B	IV	NC
418		C1	B1	IV	A	IV	B

FIG. 1BS

(72/78)

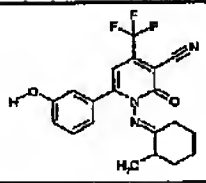
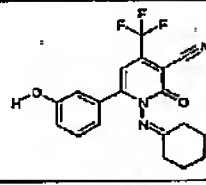
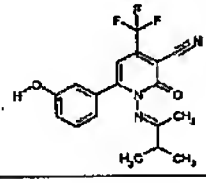
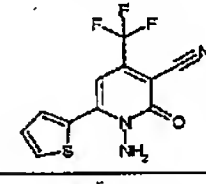
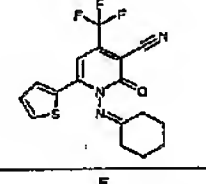
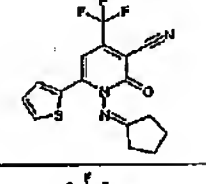
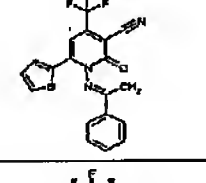
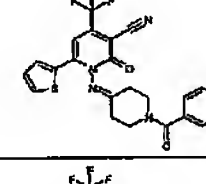
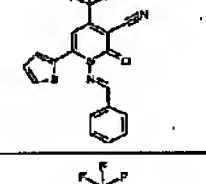
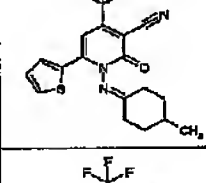
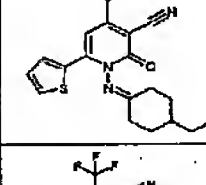
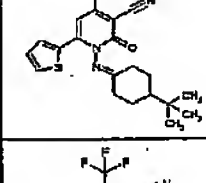
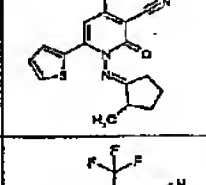
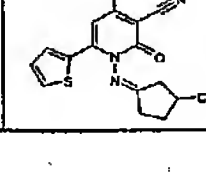
419		D1	C1	IV	A	IV	B
420		D1	C1	IV	A	IV	B
421		D1	D1	IV	A	NC	NC
422		NC	NC	NC	A	NC	NC
423		D1	D1	IV	A	NC	NC
424		NC	NC	NC	A	NC	NC
425		NC	NC	NC	A	NC	NC
426		NC	NC	NC	A	NC	NC
427		NC	NC	III	A	NC	NC
428		D1	D1	NC	A	NC	NC
429		D1	D1	NC	A	NC	NC
430		NC	NC	NC	NC	NC	NC
431		D1	D1	NC	NC	NC	NC
432		NC	NC	NC	NC	NC	NC

FIG. 1BT

(73/78)

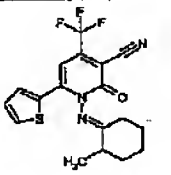
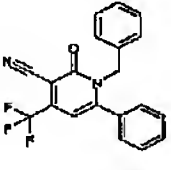
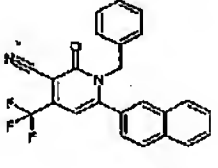
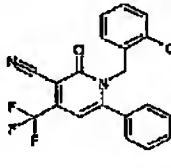
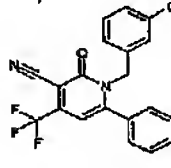
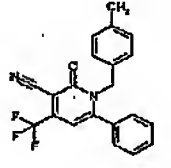
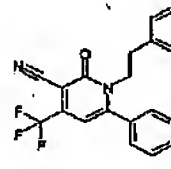
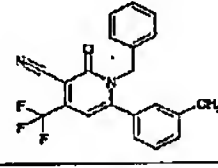
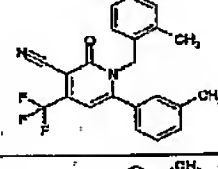
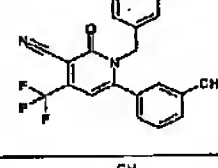
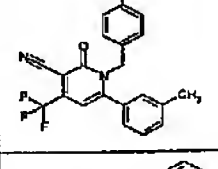
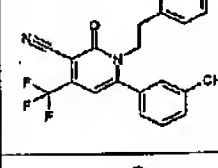
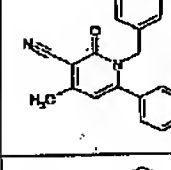
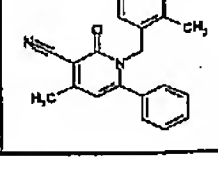
433		D1	D1	III	A	NC	NC
434		B1	B1	IV	B	IV	B
435		D1	C1	IV	A	NC	NC
436		B1	A1	IV	B	III	B
437		B1	A1	III	A	III	B
438		B1	A1	III	C	III	B
439		B1	B1	IV	B	III	B
440		B1	B1	III	B	III	B
441		B1	A1	III	B	III	B
442		B1	B1	III	B	III	B
443		B1	A1	III	C	III	B
444		B1	B1	IV	B	IV	A
445		NC	D1	NC	A	NC	NC
446		D1	B1	IV	A	NC	NC

FIG. 1BU

(74/78)

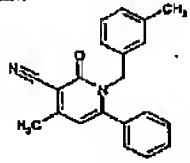
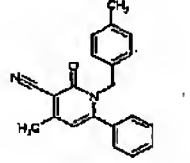
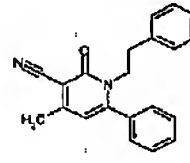
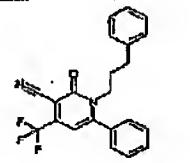
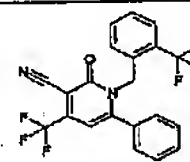
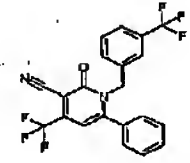
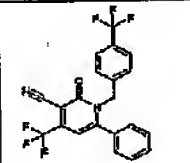
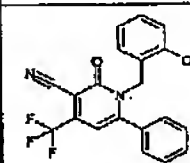
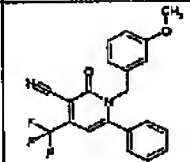
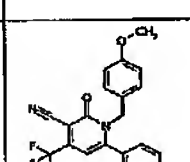
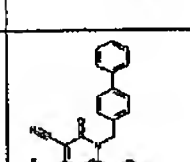
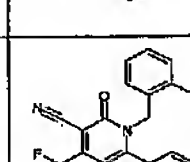
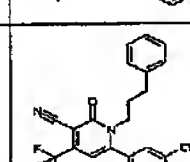
447		D1	D1	NC	NC	NC	A
448		D1	B1	IV	B	NC	NC
449		D1	D1	NC	NC	NC	A
450		D1	C1	IV	B	IV	B
451		B1	B1	IV	B	IV	B
452		C1	B1	IV	B	IV	B
453		D1	C1	IV	A	IV	B
454		B1	B1	IV	B	IV	B
455		B1	B1	IV	B	IV	B
456		B1	B1	IV	B	IV	B
457		NC	NC	NC	A	NC	A
458		B1	B1	III	B	III	B
459		D1	D1	IV	A	IV	A

FIG. 1BV

(75/78)

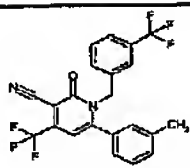
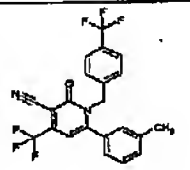
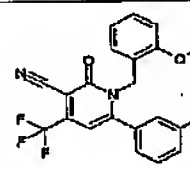
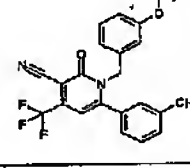
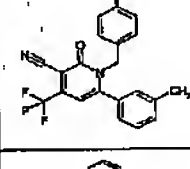
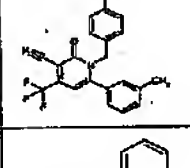
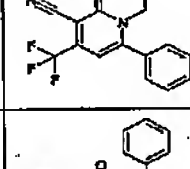
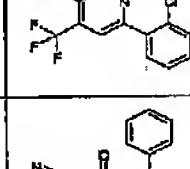
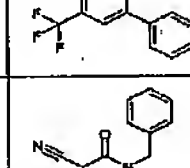
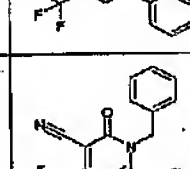
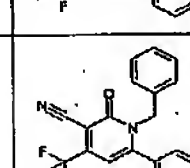
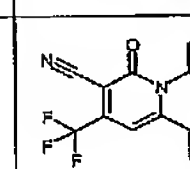
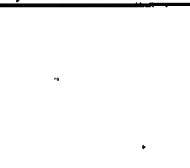
460		C1	B1	III	B	III	B
461		D1	D1	IV	A	IV	B
462		B1	B1	III	B	IV	B
463		B1	B1	III	B	III	B
464		B1	B1	III	B	III	C
465		D1	NC	NC	A	IV	A
466		B1	B1	IV	B	III	B
467		B1	B1	III	B	III	B
468		B1	A1	III	B	III	B
469		D1	C1	IV	A	IV	B
470		D1	C1	IV	A	IV	B
471		D1	B1	IV	B	IV	B
472		B1	B1	IV	B	IV	B

FIG. 1BW

(76/78)

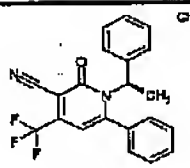
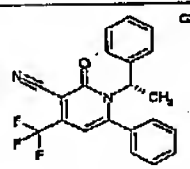
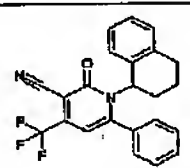
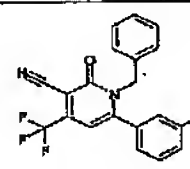
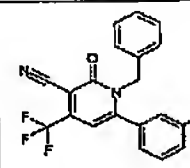
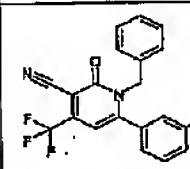
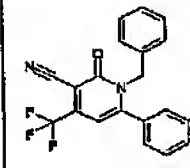
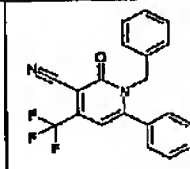
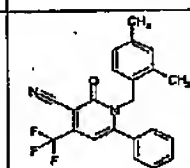
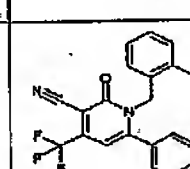
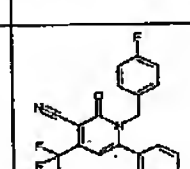
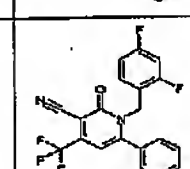
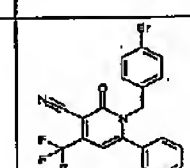
473		D1	C1	IV	A	IV	B
474		D1	C1	IV	B	IV	B
475		D1	C1	IV	A	IV	B
476		D1	C1	IV	A	III	A
477		B1	B1	III	A	III	B
478		NC	D1	NC	A	NC	A
479		D1	B1	IV	B	IV	C
480		D1	D1	NC	A	IV	B
481		B1	A1	III	C	III	B
482		B1	A1	III	B	III	B
483		B1	B1	IV	C	III	B
484		B1	A1	III	B	III	B
485		B1	B1	III	B	III	B

FIG. 1BX

(77/78)

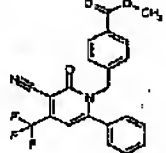
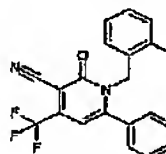
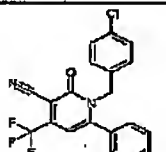
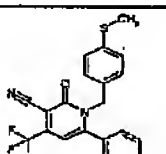
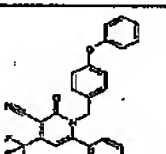
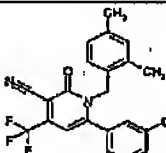
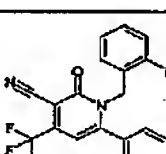
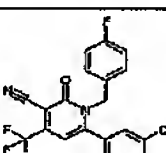
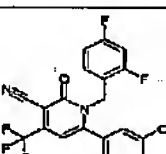
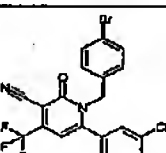
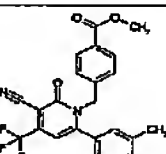
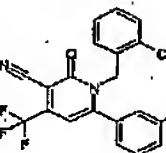
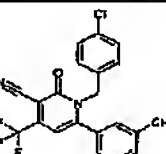
486		C1	B1	IV	B	IV	B
487		B1	B1	III	C	III	C
488		B1	A1	III	B	III	B
489		C1	B1	IV	B	III	B
490		NC	D1	NC	A	NC	A
491		A1	A1	III	C	II	B
492		B1	A1	III	B	III	B
493		B1	A1	III	B	III	B
494		B1	A1	III	B	III	B
495		B1	B1	III	C	III	B
496		B1	B1	III	C	III	B
497		B1	A1	III	B	III	B
498		B1	A1	III	C	III	B

FIG. 1BY

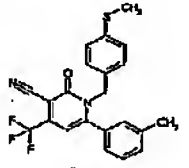
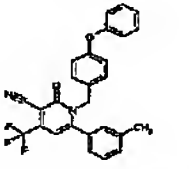
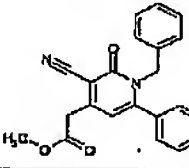
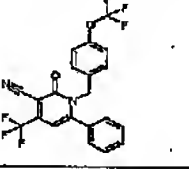
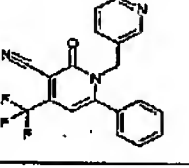
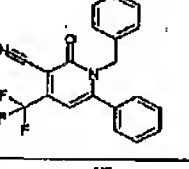
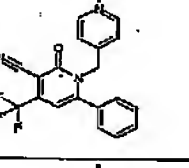
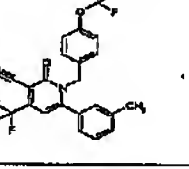
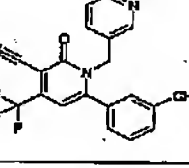
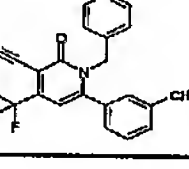
499		B1	B1	III	B	III	B
500		NC	NC	NC	A	NC	A
501		NC	NC	NC	A	NC	A
502		D1	D1	IV	A	III	A
503		NC	D1	IV	A	IV	B
504		NC	NC	NC	A	NC	A
505		B1	A1	III	B	III	C
506		D1	D1	IV	A	III	B
507		D1	D1	III	B	III	B
508		NC	NC	NC	A	NC	A

FIG. 1BZ

- 1 -

SEQUENCE LISTING

<110> X-Ceptor Therapeutics, Inc.
 Bayne Christopher D.
 Johnson Alan T.
 Lu Shao-Po
 Mohan Raju
 Griffith Ronald C.

<120> Modulators Of LXR

<130> 38205-3005PC

<140> Unassigned

<141> Herewith

<150> 60/342,707

<151> 2001-12-21

<160> 18

<170> FastSEQ for Windows Version 4.0

<210> 1

<211> 1528

<212> DNA

<213> Homo Sapien

<220>

<221> CDS

<222> (36) ... (1379)

<300>

<308> GeneBank Nm_005693

<309> 2002-05-14

<400> 1

```

cagtgccttg gtaatgacca gggctccaga aagag atg tcc ttg tgg ctg ggg      53
                               Met Ser Leu Trp Leu Gly
                               1           5

gcc cct gtg cct gac att cct cct gac tct gcg gtg gag ctg tgg aag      101
Ala Pro Val Pro Asp Ile Pro Pro Asp Ser Ala Val Glu Leu Trp Lys
                10                15                20

cca ggc gca cag gat gca agc agc cag gcc cag gga ggc agc agc tgc      149
Pro Gly Ala Gln Asp Ala Ser Ser Gln Ala Gln Gly Gly Ser Ser Cys
                25                30                35

atc ctc aga gag gaa gcc agg atg ccc cac tct gct ggg ggt act gca      197
Ile Leu Arg Glu Glu Ala Arg Met Pro His Ser Ala Gly Gly Thr Ala
                40                45                50

ggg gtg ggg ctg gag gct gca gag ccc aca gcc ctg ctc acc agg gca      245
Gly Val Gly Leu Glu Ala Ala Glu Pro Thr Ala Leu Leu Thr Arg Ala
                55                60                65                70

gag ccc cct tca gaa ccc aca gag atc cgt cca caa aag cgg aaa aag      293
Glu Pro Pro Ser Glu Pro Thr Glu Ile Arg Pro Gln Lys Arg Lys Lys
                75                80                85

ggg cca gcc ccc aaa atg ctg ggg aac gag cta tgc agc gtg tgt ggg      341
Gly Pro Ala Pro Lys Met Leu Gly Asn Glu Leu Cys Ser Val Cys Gly
                90                95                100

```

- 2 -

gac aag gcc tcg ggc ttc cac tac aat gtt ctg agc tgc gag ggc tgc	389
Asp Lys Ala Ser Gly Phe His Tyr Asn Val Leu Ser Cys Glu Gly Cys	
105 110 115	
aag gga ttc ttc cgc cgc agc gtc atc aag gga gcg cac tac atc tgc	437
Lys Gly Phe Phe Arg Arg Ser Val Ile Lys Gly Ala His Tyr Ile Cys	
120 125 130	
cac agt ggc ggc cac tgc ccc atg gac acc tac atg cgt cgc aag tgc	485
His Ser Gly Gly His Cys Pro Met Asp Thr Tyr Met Arg Arg Lys Cys	
135 140 145 150	
cag gag tgt cgg ctt cgc aaa tgc cgt cag gct ggc atg cgg gag gag	533
Gln Glu Cys Arg Leu Arg Lys Cys Arg Gln Ala Gly Met Arg Glu Glu	
155 160 165	
tgt gtc ctg tca gaa gaa cag atc cgc ctg aag aaa ctg aag cgg caa	581
Cys Val Leu Ser Glu Glu Gln Ile Arg Leu Lys Lys Leu Lys Arg Gln	
170 175 180	
gag gag gaa cag gct cat gcc aca tcc ttg ccc ccc agg cgt tcc tca	629
Glu Glu Glu Gln Ala His Ala Thr Ser Leu Pro Pro Arg Arg Ser Ser	
185 190 195	
ccc ccc caa atc ctg ccc cag ctc agc ccg gaa caa ctg ggc atg atc	677
Pro Pro Gln Ile Leu Pro Gln Leu Ser Pro Glu Gln Leu Gly Met Ile	
200 205 210	
gag aag ctc gtc gct gcc cag caa cag tgt aac cgg cgc tcc ttt tct	725
Glu Lys Leu Val Ala Ala Gln Gln Gln Cys Asn Arg Arg Ser Phe Ser	
215 220 225 230	
gac cgg ctt cga gtc acg cct tgg ccc atg gca cca gat ccc cat agc	773
Asp Arg Leu Arg Val Thr Pro Trp Pro Met Ala Pro Asp Pro His Ser	
235 240 245	
cgg gag gcc cgt cag cag cgc ttt gcc cac ttc act gag ctg gcc atc	821
Arg Glu Ala Arg Gln Gln Arg Phe Ala His Phe Thr Glu Leu Ala Ile	
250 255 260	
gtc tct gtg cag gag ata gtt gac ttt gct aaa cag cta ccc ggc ttc	869
Val Ser Val Gln Glu Ile Val Asp Phe Ala Lys Gln Leu Pro Gly Phe	
265 270 275	
ctg cag ctc agc cgg gag gac cag att gcc ctg ctg aag acc tct gcg	917
Leu Gln Leu Ser Arg Glu Asp Gln Ile Ala Leu Leu Lys Thr Ser Ala	
280 285 290	
atc gag gtg atg ctt ctg gag aca tct cgg agg tac aac cct ggg agt	965
Ile Glu Val Met Leu Leu Glu Thr Ser Arg Arg Tyr Asn Pro Gly Ser	
295 300 305 310	
gag agt atc acc ttc ctc aag gat ttc agt tat aac cgg gaa gac ttt	1013
Glu Ser Ile Thr Phe Leu Lys Asp Phe Ser Tyr Asn Arg Glu Asp Phe	
315 320 325	
gcc aaa gca ggg ctg caa gtg gaa ttc atc aac ccc atc ttc gag ttc	1061
Ala Lys Ala Gly Leu Gln Val Glu Phe Ile Asn Pro Ile Phe Glu Phe	
330 335 340	
tcc agg gcc atg aat gag ctg caa ctc aat gat gcc gag ttt gcc ttg	1109
Ser Arg Ala Met Asn Glu Leu Gln Leu Asn Asp Ala Glu Phe Ala Leu	
345 350 355	
ctc att gct atc agc atc ttc tct gca gac cgg ccc aac gtg cag gac	1157
Leu Ile Ala Ile Ser Ile Phe Ser Ala Asp Arg Pro Asn Val Gln Asp	
360 365 370	

- 3 -

```

cag ctc cag gtg gag agg ctg cag cac aca tat gtg gaa gcc ctg cat 1205
Gln Leu Gln Val Glu Arg Leu Gln His Thr Tyr Val Glu Ala Leu His
375 380 385 390

gcc tac gtc tcc atc cac cat ccc cat gac cga ctg atg ttc cca cgg 1253
Ala Tyr Val Ser Ile His His Pro His Asp Arg Leu Met Phe Pro Arg
400 405

atg cta atg aaa ctg gtg agc ctc cgg acc ctg agc agc gtc cac tca 1301
Met Leu Met Lys Leu Val Ser Leu Arg Thr Leu Ser Ser Val His Ser
410 415 420

gag caa gtg ttt gca ctg cgt ctg cag gac aaa aag ctc cca ccg ctg 1349
Gln Gln Val Phe Ala Leu Arg Leu Gln Asp Lys Lys Leu Pro Pro Leu
425 430 435

ctc tct gag atc tgg gat gtg cac gaa tga ctgttctgtc cccatatttt 1399
Leu Ser Glu Ile Trp Asp Val His Glu *
440 445

ctgtttttctt ggccggatgg ctgaggcctg gtggctgcct cctagaagtg gaacagactg 1459
agaagggcaa acattcctgg gagctgggca aggagatcct cccgtggcat taaaagagag 1519
tcaaagggt 1528

```

<210> 2
 <211> 447
 <212> PRT
 <213> Homo Sapien

```

<400> 2
Met Ser Leu Trp Leu Gly Ala Pro Val Pro Asp Ile Pro Pro Asp Ser
1 5 10 15
Ala Val Glu Leu Trp Lys Pro Gly Ala Gln Asp Ala Ser Ser Gln Ala
20 25 30
Gln Gly Gly Ser Ser Cys Ile Leu Arg Glu Glu Ala Arg Met Pro His
35 40 45
Ser Ala Gly Gly Thr Ala Gly Val Gly Leu Glu Ala Ala Glu Pro Thr
50 55 60
Ala Leu Leu Thr Arg Ala Glu Pro Pro Ser Glu Pro Thr Glu Ile Arg
65 70 75 80
Pro Gln Lys Arg Lys Lys Gly Pro Ala Pro Lys Met Leu Gly Asn Glu
85 90 95
Leu Cys Ser Val Cys Gly Asp Lys Ala Ser Gly Phe His Tyr Asn Val
100 105 110
Leu Ser Cys Glu Gly Cys Lys Gly Phe Phe Arg Arg Ser Val Ile Lys
115 120 125
Gly Ala His Tyr Ile Cys His Ser Gly Gly His Cys Pro Met Asp Thr
130 135 140
Tyr Met Arg Arg Lys Cys Gln Glu Cys Arg Leu Arg Lys Cys Arg Gln
145 150 155 160
Ala Gly Met Arg Glu Glu Cys Val Leu Ser Glu Glu Gln Ile Arg Leu
165 170 175
Lys Lys Leu Lys Arg Gln Glu Glu Glu Gln Ala His Ala Thr Ser Leu
180 185 190
Pro Pro Arg Arg Ser Ser Pro Pro Gln Ile Leu Pro Gln Leu Ser Pro
195 200 205
Glu Gln Leu Gly Met Ile Glu Lys Leu Val Ala Ala Gln Gln Gln Cys
210 215 220
Asn Arg Arg Ser Phe Ser Asp Arg Leu Arg Val Thr Pro Trp Pro Met
225 230 235 240
Ala Pro Asp Pro His Ser Arg Glu Ala Arg Gln Gln Arg Phe Ala His
245 250 255
Phe Thr Glu Leu Ala Ile Val Ser Val Gln Glu Ile Val Asp Phe Ala
260 265 270
Lys Gln Leu Pro Gly Phe Leu Gln Leu Ser Arg Glu Asp Gln Ile Ala
275 280 285

```

- 4 -

Leu	Leu	Lys	Thr	Ser	Ala	Ile	Glu	Val	Met	Leu	Leu	Glu	Thr	Ser	Arg
290						295				300					
Arg	Tyr	Asn	Pro	Gly	Ser	Glu	Ser	Ile	Thr	Phe	Leu	Lys	Asp	Phe	Ser
305					310					315					320
Tyr	Asn	Arg	Glu	Asp	Phe	Ala	Lys	Ala	Gly	Leu	Gln	Val	Glu	Phe	Ile
				325					330					335	
Asn	Pro	Ile	Phe	Glu	Phe	Ser	Arg	Ala	Met	Asn	Glu	Leu	Gln	Leu	Asn
			340					345					350		
Asp	Ala	Glu	Phe	Ala	Leu	Leu	Ile	Ala	Ile	Ser	Ile	Phe	Ser	Ala	Asp
		355					360					365			
Arg	Pro	Asn	Val	Gln	Asp	Gln	Leu	Gln	Val	Glu	Arg	Leu	Gln	His	Thr
370						375					380				
Tyr	Val	Glu	Ala	Leu	His	Ala	Tyr	Val	Ser	Ile	His	His	Pro	His	Asp
385					390					395					400
Arg	Leu	Met	Phe	Pro	Arg	Met	Leu	Met	Lys	Leu	Val	Ser	Leu	Arg	Thr
				405					410					415	
Leu	Ser	Ser	Val	His	Ser	Glu	Gln	Val	Phe	Ala	Leu	Arg	Leu	Gln	Asp
			420					425					430		
Lys	Lys	Leu	Pro	Pro	Leu	Leu	Ser	Glu	Ile	Trp	Asp	Val	His	Glu	
		435					440					445			

<210> 3
 <211> 1815
 <212> DNA
 <213> Homo Sapien

<220>
 <221> CDS
 <222> (56)...(1438)

<300>
 <308> GeneBank XM_046419
 <309> 2002-08-01

<400> 3
 cgctgttgct tggagagggg cgggacctgg agagaggctg ctccgtgacc ccacc atg 58
 Met
 1

tcc tct cct acc acg agt tcc ctg gat acc ccc ctg cct gga aat ggc 106
 Ser Ser Pro Thr Thr Ser Ser Leu Asp Thr Pro Leu Pro Gly Asn Gly
 5 10 15

ccc cct cag cct ggc gcc cct tct tct tca ccc act gta aag gag gag 154
 Pro Pro Gln Pro Gly Ala Pro Ser Ser Ser Pro Thr Val Lys Glu Glu
 20 25 30

ggt ccg gag ccg tgg ccc ggg ggt ccg gac cct gat gtc cca ggc act 202
 Gly Pro Glu Pro Trp Pro Gly Gly Pro Asp Pro Asp Val Pro Gly Thr
 35 40 45

gat gag gcc agc tca gcc tgc agc aca gac tgg gtc atc cca gat ccc 250
 Asp Glu Ala Ser Ser Ala Cys Ser Thr Asp Trp Val Ile Pro Asp Pro
 50 55 60 65

gaa gag gaa cca gag cgc aag cga aag aag ggc cca gcc ccg aag atg 298
 Glu Glu Glu Pro Glu Arg Lys Arg Lys Lys Gly Pro Ala Pro Lys Met
 70 75 80

ctg ggc cac gag ctt tgc cgt gtc tgt ggg gac aag gcc tcc ggc ttc 346
 Leu Gly His Glu Leu Cys Arg Val Cys Gly Asp Lys Ala Ser Gly Phe
 85 90 95

cac tac aac gtg ctc agc tgc gaa ggc tgc aag ggc ttc ttc cgg cgc 394
 His Tyr Asn Val Leu Ser Cys Glu Gly Cys Lys Gly Phe Phe Arg Arg
 100 105 110

agt Ser	gtg Val 115	gtc Val	cgt Arg	ggt Gly	ggg Gly	gcc Ala 120	agg Arg	cgc Arg	tat Tyr	gcc Ala	tgc Cys 125	cgg Arg	ggt Gly	ggc Gly	gga Gly	442
acc Thr 130	tgc Cys	cag Gln	atg Met	gac Asp	gct Ala 135	ttc Phe	atg Met	cgg Arg	cgc Arg	aag Lys 140	tgc Cys	cag Gln	cag Gln	tgc Cys	cgg Arg 145	490
ctg Leu	cgc Arg	aag Lys	tgc Cys	aag Lys 150	gag Glu	gca Ala	ggg Gly	atg Met	agg Arg 155	gag Glu	cag Gln	tgc Cys	gtc Val	ctt Leu 160	tct Ser	538
gaa Glu	gaa Glu	cag Gln	atc Ile 165	cgg Arg	aag Lys	aag Lys	aag Lys	att Ile 170	cgg Arg	aaa Lys	cag Gln	cag Gln	cag Gln 175	gag Glu	tca Ser	586
cag Gln	tca Ser	cag Gln 180	tcg Ser	cag Gln	tca Ser	cct Pro	gtg Val 185	ggg Gly	ccg Pro	cag Gln	ggc Gly	agc Ser 190	agc Ser	agc Ser	tca Ser	634
gcc Ala 195	tct Ser	ggg Gly	cct Pro	ggg Gly	gct Ala	tcc Ser 200	cct Pro	ggt Gly	gga Gly	tct Ser	gag Glu 205	gca Ala	ggc Gly	agc Ser	cag Gln	682
ggc Gly 210	tcc Ser	ggg Gly	gaa Glu	ggc Gly	gag Glu 215	ggt Gly	gtc Val	cag Gln	cta Leu	aca Thr 220	gcg Ala	gct Ala	caa Gln	gaa Glu	cta Leu 225	730
atg Met	atc Ile	cag Gln	cag Gln	ttg Leu 230	gtg Val	gcg Ala	gcc Ala	caa Gln	ctg Leu 235	cag Gln	tgc Cys	aac Asn	aaa Lys	cgc Arg 240	tcc Ser	778
ttc Phe	tcc Ser	gac Asp	cag Gln 245	ccc Pro	aaa Lys	gtc Val	acg Thr	ccc Pro 250	tgg Trp	ccc Pro	ctg Leu	ggc Gly	gca Ala 255	gac Asp	ccc Pro	826
cag Gln	tcc Ser	cga Arg 260	gat Asp	gcc Ala	cgc Arg	cag Gln	caa Gln 265	cgc Arg	ttt Phe	gcc Ala	cac His	ttc Phe 270	acg Thr	gag Glu	ctg Leu	874
gcc Ala 275	atc Ile	atc Ile	tca Ser	gtc Val	cag Gln	gag Glu 280	atc Ile	gtg Val	gac Asp	ttc Phe	gct Ala 285	aag Lys	caa Gln	gtg Val	cct Pro	922
ggt Gly 290	ttc Phe	ctg Leu	cag Gln	ctg Leu	ggc Gly 295	cgg Arg	gag Glu	gac Asp	cag Gln	atc Ile 300	gcc Ala	ctc Leu	ctg Leu	aag Lys	gca Ala 305	970
tcc Ser	act Thr	atc Ile	gag Glu	atc Ile 310	atg Met	ctg Leu	cta Leu	gag Glu	aca Thr 315	gcc Ala	agg Arg	cgc Arg	tac Tyr	aac Asn 320	cac His	1018
gag Glu	aca Thr	gag Glu	tgt Cys 325	atc Ile	acc Thr	ttc Phe	ttg Leu	aag Lys 330	gac Asp	ttc Phe	acc Thr	tac Tyr 335	agc Ser	aag Lys	gac Asp	1066
gac Asp	ttc Phe	cac His 340	cgt Arg	gca Ala	ggc Gly	ctg Leu	cag Gln 345	gtg Val	gag Glu	ttc Phe	atc Ile	aac Asn 350	ccc Pro	atc Ile	ttc Phe	1114
gag Glu 355	ttc Phe	tcg Ser	cgg Arg	gcc Ala	atg Met	cgg Arg 360	cgg Arg	ctg Leu	ggc Gly	ctg Leu	gac Asp 365	gac Asp	gct Ala	gag Glu	tac Tyr	1162
gcc Ala	ctg Leu	ctc Leu	atc Ile	gcc Ala	atc Ile	aac Asn	atc Ile	ttc Phe	tcg Ser	gcc Ala	gac Asp	cgg Arg	ccc Pro	aac Asn	gtg Val	1210

- 6 -

370 375 380 385

cag gag ccg ggc cgc gtg gag gcg ttg cag cag ccc tac gtg gag gcg 1258
Gln Glu Pro Gly Arg Val Glu Ala Leu Gln Gln Pro Tyr Val Glu Ala
390 395 400

ctg ctg tcc tac acg cgc atc aag agg ccg cag gac cag ctg cgc ttc 1306
Leu Leu Ser Tyr Thr Arg Ile Lys Arg Pro Gln Asp Gln Leu Arg Phe
405 410 415

ccg cgc atg ctc atg aag ctg gtg agc ctg cgc acg ctg agc tct gtg 1354
Pro Arg Met Leu Met Lys Leu Val Ser Leu Arg Thr Leu Ser Ser Val
420 425 430

cac tcg gag cag gtc ttc gcc ttg cgg ctc cag gac aag aag ctg ccg 1402
His Ser Glu Gln Val Phe Ala Leu Arg Leu Gln Asp Lys Lys Leu Pro
435 440 445

cct ctg ctg tcg gag atc tgg gac gtc cac gag tga ggggctggcc 1448
Pro Leu Leu Ser Glu Ile Trp Asp Val His Glu *
450 455 460

accagcccc acagccttgc ctgaccaccc tccagcagat agacgccggc accccttcct 1508
cttcctaggg tggaaggggc cctgggcccga gcctgtagac ctatcggctc tcatcccttg 1568
ggataagccc cagtcagggt ccaggaggct ccctccctgc ccagcagatc ttccagaagg 1628
ggtgaaaggg ttgcagggtc cgaccactga cccttcccgg ctgccctccc tccccagctt 1688
acacctcaag cccagcacgc agtgcacctt gaacagaggg aggggaggac ccatggctct 1748
ccccctagc ccgggagacc agggccttcc tcttctctg cttttattta ataaaaacta 1808
aaaacag 1815

<210> 4
<211> 460
<212> PRT
<213> Homo Sapien

<400> 4

Met Ser Ser Pro Thr Thr Ser Ser Leu Asp Thr Pro Leu Pro Gly Asn
1 5 10 15
Gly Pro Pro Gln Pro Gly Ala Pro Ser Ser Ser Pro Thr Val Lys Glu
20 25 30
Glu Gly Pro Glu Pro Trp Pro Gly Gly Pro Asp Pro Asp Val Pro Gly
35 40 45
Thr Asp Glu Ala Ser Ser Ala Cys Ser Thr Asp Trp Val Ile Pro Asp
50 55 60
Pro Glu Glu Glu Pro Glu Arg Lys Arg Lys Lys Gly Pro Ala Pro Lys
65 70 75 80
Met Leu Gly His Glu Leu Cys Arg Val Cys Gly Asp Lys Ala Ser Gly
85 90 95
Phe His Tyr Asn Val Leu Ser Cys Glu Gly Cys Lys Gly Phe Phe Arg
100 105 110
Arg Ser Val Val Arg Gly Gly Ala Arg Arg Tyr Ala Cys Arg Gly Gly
115 120 125
Gly Thr Cys Gln Met Asp Ala Phe Met Arg Arg Lys Cys Gln Gln Cys
130 135 140
Arg Leu Arg Lys Cys Lys Glu Ala Gly Met Arg Glu Gln Cys Val Leu
145 150 155 160
Ser Glu Glu Gln Ile Arg Lys Lys Lys Ile Arg Lys Gln Gln Gln Glu
165 170 175
Ser Gln Ser Gln Ser Gln Ser Pro Val Gly Pro Gln Gly Ser Ser Ser
180 185 190
Ser Ala Ser Gly Pro Gly Ala Ser Pro Gly Gly Ser Glu Ala Gly Ser
195 200 205
Gln Gly Ser Gly Glu Gly Glu Gly Val Gln Leu Thr Ala Ala Gln Glu
210 215 220
Leu Met Ile Gln Gln Leu Val Ala Ala Gln Leu Gln Cys Asn Lys Arg
225 230 235 240
Ser Phe Ser Asp Gln Pro Lys Val Thr Pro Trp Pro Leu Gly Ala Asp

- 7 -

Pro	Gln	Ser	Arg	245	Asp	Ala	Arg	Gln	Gln	250	Arg	Phe	Ala	His	Phe	255	Thr	Glu
Leu	Ala	Ile	Ile	260	Ser	Val	Gln	Glu	Ile	265	Val	Asp	Phe	Ala	Lys	Gln	Val	
Pro	Gly	Phe	Leu	275	Gln	Leu	Gly	Arg	Glu	280	Asp	Gln	Ile	Ala	Leu	Leu	Lys	
Ala	Ser	Thr	Ile	290	Glu	Ile	Met	Leu	Leu	295	Glu	Thr	Ala	Arg	Arg	Tyr	Asn	
His	Glu	Thr	Glu	305	Cys	Ile	Thr	Phe	Leu	310	Lys	Asp	Phe	Thr	Tyr	Ser	Lys	
Asp	Asp	Phe	His	325	Arg	Ala	Gly	Leu	Gln	330	Val	Glu	Phe	Ile	Asn	Pro	Ile	
Phe	Glu	Phe	Ser	340	Arg	Ala	Met	Arg	Arg	345	Leu	Gly	Leu	Asp	Asp	Ala	Glu	
Tyr	Ala	Leu	Leu	355	Ile	Ala	Ile	Asn	Ile	360	Phe	Ser	Ala	Asp	Arg	Pro	Asn	
Val	Gln	Glu	Pro	370	Gly	Arg	Val	Glu	Ala	375	Leu	Gln	Gln	Pro	Tyr	Val	Glu	
Ala	Leu	Leu	Ser	385	Tyr	Thr	Arg	Ile	Lys	390	Arg	Pro	Gln	Asp	Gln	Leu	Arg	
Phe	Pro	Arg	Met	405	Leu	Met	Lys	Leu	Val	410	Ser	Leu	Arg	Thr	Leu	Ser	Ser	
Val	His	Ser	Glu	420	Gln	Val	Phe	Ala	Leu	425	Arg	Leu	Gln	Asp	Lys	Lys	Leu	
Pro	Pro	Leu	Leu	435	Ser	Glu	Ile	Trp	Asp	440	Val	His	Glu	445				
				450			455						460					

<210> 5
 <211> 2070
 <212> DNA
 <213> Rattus norvegicus

<220>
 <221> CDS
 <222> (172) ... (1581)

<300>
 <308> GeneBank U18374
 <309> 1995-06-21

<400> 5
 ctgagttctg agcgtctaca gcgaaagtgc tgggcttttg aaaggagacc tgggctccga 60
 atcctctcag ggccttggac gtctctgacc caaaacaatc caagggttctt atttgaagac 120
 caccatccca gaagcacatt ctcgagttga aaagttggag tgggtgttcga a atg aat 177
 Met Asn
 1

ctg att ggg ccc tcc cat tta caa gcc acg gac gag ttt gct ctt tct 225
 Leu Ile Gly Pro Ser His Leu Gln Ala Thr Asp Glu Phe Ala Leu Ser
 5 10 15

gaa aac tta ttt gga gtg cta aca gag cac gcg gca ggt cct ctg ggg 273
 Glu Asn Leu Phe Gly Val Leu Thr Glu His Ala Ala Gly Pro Leu Gly
 20 25 30

cag aat ctg gac ttg gaa tcg tac tcc cca tac aac aat gtg cag ttt 321
 Gln Asn Leu Asp Leu Glu Ser Tyr Ser Pro Tyr Asn Asn Val Gln Phe
 35 40 45 50

cct caa gtt cag cca cag atc tcc tcc tcg tcc tat tat tcc aac ctg 369
 Pro Gln Val Gln Pro Gln Ile Ser Ser Ser Ser Tyr Tyr Ser Asn Leu
 55 60 65

ggg ttc tac ccg caa caa ccg gaa gac tgg tac tct cct gga ctc tat 417
 Gly Phe Tyr Pro Gln Gln Pro Glu Asp Trp Tyr Ser Pro Gly Leu Tyr

- 8 -

70				75				80								
gaa	ctc	agg	cga	atg	ccc	act	gag	agt	gtg	tac	cag	gga	gag	act	gag	465
Glu	Leu	Arg	Arg	Met	Pro	Thr	Glu	Ser	Val	Tyr	Gln	Gly	Glu	Thr	Glu	
		85					90					95				
gta	tcc	gag	atg	cct	gtg	aca	aag	aag	ccg	cga	atg	gcc	gcc	tca	tcg	513
Val	Ser	Glu	Met	Pro	Val	Thr	Lys	Lys	Pro	Arg	Met	Ala	Ala	Ser	Ser	
	100					105					110					
gcg	gga	aga	ata	aaa	ggg	gat	gag	ctg	tgt	gtg	gtc	tgc	gga	gac	agg	561
Ala	Gly	Arg	Ile	Lys	Gly	Asp	Glu	Leu	Cys	Val	Val	Cys	Gly	Asp	Arg	
115					120					125					130	
gcc	tct	ggg	tac	cat	tac	aac	gcg	ctc	acc	tgc	gag	ggc	tgc	aaa	ggt	609
Ala	Ser	Gly	Tyr	His	Tyr	Asn	Ala	Leu	Thr	Cys	Glu	Gly	Cys	Lys	Gly	
				135					140					145		
ttc	ttc	cga	aga	agc	atc	acc	aaa	aac	gcc	gtg	tac	aag	tgt	aag	aac	657
Phe	Phe	Arg	Arg	Ser	Ile	Thr	Lys	Asn	Ala	Val	Tyr	Lys	Cys	Lys	Asn	
		150					155						160			
ggg	ggc	aac	tgc	gtg	atg	gat	atg	tac	atg	cgt	cgg	aag	tgc	cag	gat	705
Gly	Gly	Asn	Cys	Val	Met	Asp	Met	Tyr	Met	Arg	Arg	Lys	Cys	Gln	Asp	
		165				170						175				
tgc	cgg	cta	agg	aag	tgc	aga	gag	atg	gga	atg	ttg	gct	gaa	tgt	ttg	753
Cys	Arg	Leu	Arg	Lys	Cys	Arg	Glu	Met	Gly	Met	Leu	Ala	Glu	Cys	Leu	
	180					185					190					
tta	act	gaa	att	cag	tgt	aaa	tct	aaa	cgg	cta	agg	aaa	aat	gtg	aag	801
Leu	Thr	Glu	Ile	Gln	Cys	Lys	Ser	Lys	Arg	Leu	Arg	Lys	Asn	Val	Lys	
195					200					205					210	
cag	cat	gcg	gat	cag	aca	gtg	aat	gag	gac	agc	gaa	ggg	cgt	gac	ttg	849
Gln	His	Ala	Asp	Gln	Thr	Val	Asn	Glu	Asp	Ser	Glu	Gly	Arg	Asp	Leu	
				215					220					225		
cgg	caa	gtg	acc	tcc	acg	acc	aag	cta	tgc	agg	gag	aaa	act	gaa	ctc	897
Arg	Gln	Val	Thr	Ser	Thr	Thr	Lys	Leu	Cys	Arg	Glu	Lys	Thr	Glu	Leu	
			230					235					240			
act	gta	gac	cag	cag	acc	ctc	ctg	gat	tat	att	atg	gac	tca	tac	agc	945
Thr	Val	Asp	Gln	Gln	Thr	Leu	Leu	Asp	Tyr	Ile	Met	Asp	Ser	Tyr	Ser	
		245					250					255				
aaa	cag	aga	atg	cca	cag	gag	atc	aca	aat	aaa	atc	tta	aaa	gaa	gaa	993
Lys	Gln	Arg	Met	Pro	Gln	Glu	Ile	Thr	Asn	Lys	Ile	Leu	Lys	Glu	Glu	
	260					265					270					
ttt	agt	gca	gaa	gaa	aat	ttt	ctc	ata	tta	aca	gaa	atg	gct	acc	agt	1041
Phe	Ser	Ala	Glu	Glu	Asn	Phe	Leu	Ile	Leu	Thr	Glu	Met	Ala	Thr	Ser	
275					280					285					290	
cac	gta	cag	att	ctc	gta	gaa	ttc	aca	aaa	aga	ctt	cca	ggg	ttt	cag	1089
His	Val	Gln	Ile	Leu	Val	Glu	Phe	Thr	Lys	Arg	Leu	Pro	Gly	Phe	Gln	
				295					300					305		
aca	ctg	gac	cac	gaa	gac	cag	att	gct	ttg	ctc	aaa	ggg	tcc	gca	gtc	1137
Thr	Leu	Asp	His	Glu	Asp	Gln	Ile	Ala	Leu	Leu	Lys	Gly	Ser	Ala	Val	
			310					315					320			
gag	gcc	atg	ttc	ctt	cgt	tca	gcg	gag	att	ttc	aat	aag	aaa	ctt	cct	1185
Glu	Ala	Met	Phe	Leu	Arg	Ser	Ala	Glu	Ile	Phe	Asn	Lys	Lys	Leu	Pro	
		325					330					335				
gcc	gga	cac	gca	gac	ctg	ttg	gaa	gaa	aga	att	cga	aag	agc	ggc	atc	1233

- 9 -

Ala	Gly	His	Ala	Asp	Leu	Leu	Glu	Glu	Arg	Ile	Arg	Lys	Ser	Gly	Ile		
340						345					350						
tcc	gat	gag	tac	ata	acc	ccg	atg	ttt	agt	ttc	tat	aaa	agt	gtc	ggg	1281	
Ser	Asp	Glu	Tyr	Ile	Thr	Pro	Met	Phe	Ser	Phe	Tyr	Lys	Ser	Val	Gly		
355					360			365							370		
gag	ctg	aaa	atg	acc	cag	gaa	gag	tac	gct	ctg	ctc	aca	gca	att	gtc	1329	
Glu	Leu	Lys	Met	Thr	Gln	Glu	Glu	Tyr	Ala	Leu	Leu	Thr	Ala	Ile	Val		
				375				380						385			
atc	ctc	tct	cca	gac	aga	caa	tac	ata	aag	gat	aga	gag	gca	gtg	gag	1377	
Ile	Leu	Ser	Pro	Asp	Arg	Gln	Tyr	Ile	Lys	Asp	Arg	Glu	Ala	Val	Glu		
			390					395					400				
aag	ctt	cag	gag	cct	ctg	ctc	gat	gtc	cta	caa	aaa	ctc	tgc	aag	atc	1425	
Lys	Leu	Gln	Glu	Pro	Leu	Leu	Asp	Val	Leu	Gln	Lys	Leu	Cys	Lys	Ile		
		405					410					415					
tac	cag	ccc	gag	aac	cct	cag	cat	ttc	gcc	tgc	ctc	ctg	ggg	cgc	ctg	1473	
Tyr	Gln	Pro	Glu	Asn	Pro	Gln	His	Phe	Ala	Cys	Leu	Leu	Gly	Arg	Leu		
	420					425					430						
aca	gaa	ctc	cgg	aca	ttc	aac	cat	cac	cac	gct	gag	atg	ctg	atg	tct	1521	
Thr	Glu	Leu	Arg	Thr	Phe	Asn	His	His	His	Ala	Glu	Met	Leu	Met	Ser		
435					440					445					450		
tgg	agg	gtg	aat	gac	cac	aag	ttc	acc	ccg	ctc	ctc	tgt	gag	atc	tgg	1569	
Trp	Arg	Val	Asn	Asp	His	Lys	Phe	Thr	Pro	Leu	Leu	Cys	Glu	Ile	Trp		
				455				460					465				
gat	gtg	cag	tga	aggacacggg	gagaggctag	ctccttgtcc	tcctcagagc									1621	
Asp	Val	Gln	*														

agcaacctgg	tattggactt	cccttctttt	catttgtacc	aggtctcact	caagaatctc	1681	
aatgaatatt	tatgtggcaa	ttatacaatt	cccacaactg	taaatacagg	ctccatagaa	1741	
ttgcttcccc	tacactgtat	tttacaaggc	ttcgggaaac	cccactgaca	cgcccttttt	1801	
gcctcattaa	atcaattggt	acttcaattt	tgtcaactga	gctagggacc	gcctcgtttt	1861	
atcctccatg	cggcaacatt	atatatatat	atattttatc	aaatagctgt	tttctcttcc	1921	
tttttttttt	tttttttttt	cggagctggg	gactgaaccc	agggccttgc	gcttgctagg	1981	
caagcgctct	accactgagc	taaatcccca	accctatta	aatagctgtt	ttcaactgag	2041	
acaataaact	gaacgtaatg	ccaagagaa				2070	

<210> 6

<211> 469

<212> PRT

<213> Rattus norvegicus

<400> 6

Met	Asn	Leu	Ile	Gly	Pro	Ser	His	Leu	Gln	Ala	Thr	Asp	Glu	Phe	Ala		
1				5					10					15			
Leu	Ser	Glu	Asn	Leu	Phe	Gly	Val	Leu	Thr	Glu	His	Ala	Ala	Gly	Pro		
			20					25					30				
Leu	Gly	Gln	Asn	Leu	Asp	Leu	Glu	Ser	Tyr	Ser	Pro	Tyr	Asn	Asn	Val		
		35					40					45					
Gln	Phe	Pro	Gln	Val	Gln	Pro	Gln	Ile	Ser	Ser	Ser	Ser	Tyr	Tyr	Ser		
	50					55					60						
Asn	Leu	Gly	Phe	Tyr	Pro	Gln	Gln	Pro	Glu	Asp	Trp	Tyr	Ser	Pro	Gly		
65					70					75					80		
Leu	Tyr	Glu	Leu	Arg	Arg	Met	Pro	Thr	Glu	Ser	Val	Tyr	Gln	Gly	Glu		
			85						90					95			
Thr	Glu	Val	Ser	Glu	Met	Pro	Val	Thr	Lys	Lys	Pro	Arg	Met	Ala	Ala		
			100					105					110				
Ser	Ser	Ala	Gly	Arg	Ile	Lys	Gly	Asp	Glu	Leu	Cys	Val	Val	Cys	Gly		
		115				120						125					
Asp	Arg	Ala	Ser	Gly	Tyr	His	Tyr	Asn	Ala	Leu	Thr	Cys	Glu	Gly	Cys		

-10-

130	Lys Gly Phe Phe Arg Arg	135	Ser Ile Thr Lys Asn	140	Ala Val Tyr Lys Cys
145	Lys Asn Gly Gly Asn Cys	150	Val Met Asp Met Tyr	155	Met Arg Arg Lys Cys
	165	170	Arg Glu Met Gly Met	175	Leu Ala Glu
Gln Asp Cys Arg Leu Arg	Lys Cys Arg Glu Met	185	Lys Ser Lys Arg	190	Leu Arg Lys Asn
180	195	200	205		
Cys Leu Leu Thr Glu Ile Gln	Cys Lys Ser Lys Arg	210	215	220	
Val Lys Gln His Ala Asp	Gln Thr Val Asn Glu	225	230	235	
Asp Leu Arg Gln Val Thr	Ser Thr Thr Lys Leu	240	245	250	
Glu Leu Thr Val Asp	Gln Gln Thr Leu Leu	255	260	265	
Tyr Ser Lys Gln Arg Met	Pro Gln Glu Ile Thr	270	275	280	
Glu Glu Phe Ser Ala Glu	Glu Asn Phe Leu Ile	285	290	295	
Thr Ser His Val Gln Ile	Leu Val Glu Phe Thr	300	305	310	
Phe Gln Thr Leu Asp	His Glu Asp Gln Ile	315	320	325	
Ala Val Glu Ala Met	Phe Leu Arg Ser Ala	330	335	340	
Leu Pro Ala Gly His	Ala Asp Leu Leu Glu	345	350	355	
Gly Ile Ser Asp Glu Tyr	Ile Thr Pro Met Phe	360	365	370	
Val Gly Glu Leu Lys Met	Thr Gln Glu Glu Tyr	375	380	385	
Ile Val Ile Leu Ser	Pro Asp Arg Gln Tyr	390	395	400	
Val Glu Lys Leu Gln	Glu Pro Leu Leu Asp	405	410	415	
Lys Ile Tyr Gln Pro	Glu Asn Pro Gln His	420	425	430	
Arg Leu Thr Glu Leu	Arg Thr Phe Asn His	435	440	445	
Met Ser Trp Arg Val	Asn Asp His Lys Phe	450	455	460	
Ile Trp Asp Val Gln					
465					

<210> 7
 <211> 2218
 <212> DNA
 <213> Homo Sapien

<220>
 <221> CDS
 <222> (354) ... (1772)

<300>
 <308> GeneBank NM_005123
 <309> 2002-11-05

<400> 7
 acgagactct ctctctctcc tcacctcatt gtctccccga cttatcctaa tgcgaaattg 60
 gattctgagc atttgtagca aaatcgctgg gatctggaga ggaagactca gtccagaatc 120
 ctcccagggc cttgaaagtc catctctgac ccaaaacaat ccaaggaggt agaagacatc 180
 gtagaaggag tgaaagaaga aaagaagact tagaaacata gctcaaagtg aacactgctt 240
 ctcttagttt cctggatttc ttctggacat ttcctcaaga tgaaacttca gacactttgg 300
 agtttttttt gaagaccacc ataaagaaag tgcattttcaa ttgaaaaatt tgg atg 356
 Met
 1

-11-

gga tca aaa atg aat ctc att gaa cat tcc cat tta cct acc aca gat	404
Gly Ser Lys Met Asn Leu Ile Glu His Ser His Leu Pro Thr Thr Asp	
5 10 15	
gaa ttt tct ttt tct gaa aat tta ttt ggt gtt tta aca gaa caa gtg	452
Glu Phe Ser Phe Ser Glu Asn Leu Phe Gly Val Leu Thr Glu Gln Val	
20 25 30	
gca ggt cct ctg gga cag aac ctg gaa gtg gaa cca tac tcg caa tac	500
Ala Gly Pro Leu Gly Gln Asn Leu Glu Val Glu Pro Tyr Ser Gln Tyr	
35 40 45	
agc aat gtt cag ttt ccc caa gtt caa cca cag att tcc tcg tca tcc	548
Ser Asn Val Gln Phe Pro Gln Val Gln Pro Gln Ile Ser Ser Ser Ser	
50 55 60 65	
tat tat tcc aac ctg ggt ttc tac ccc cag cag cct gaa gag tgg tac	596
Tyr Tyr Ser Asn Leu Gly Phe Tyr Pro Gln Gln Pro Glu Glu Trp Tyr	
70 75 80	
tct cct gga ata tat gaa ctc agg cgt atg cca gct gag act ctc tac	644
Ser Pro Gly Ile Tyr Glu Leu Arg Arg Met Pro Ala Glu Thr Leu Tyr	
85 90 95	
cag gga gaa act gag gta gca gag atg cct gta aca aag aag ccc cgc	692
Gln Gly Glu Thr Glu Val Ala Glu Met Pro Val Thr Lys Lys Pro Arg	
100 105 110	
atg ggc gcg tca gca ggg agg atc aaa ggg gat gag ctg tgt gtt gtt	740
Met Gly Ala Ser Ala Gly Arg Ile Lys Gly Asp Glu Leu Cys Val Val	
115 120 125	
tgt gga gac aga gcc tct gga tac cac tat aat gca ctg acc tgt gag	788
Cys Gly Asp Arg Ala Ser Gly Tyr His Tyr Asn Ala Leu Thr Cys Glu	
130 135 140 145	
ggg tgt aaa ggt ttc ttc agg aga agc att acc aaa aac gct gtg tac	836
Gly Cys Lys Gly Phe Phe Arg Arg Ser Ile Thr Lys Asn Ala Val Tyr	
150 155 160	
aag tgt aaa aac ggg ggc aac tgt gtg atg gat atg tac atg cga aga	884
Lys Cys Lys Asn Gly Gly Asn Cys Val Met Asp Met Tyr Met Arg Arg	
165 170 175	
aag tgt caa gag tgt cga cta agg aaa tgc aaa gag atg gga atg ttg	932
Lys Cys Gln Glu Cys Arg Leu Arg Lys Cys Lys Glu Met Gly Met Leu	
180 185 190	
gct gaa tgc ttg tta act gaa att cag tgt aaa tct aag cga ctg aga	980
Ala Glu Cys Leu Leu Thr Glu Ile Gln Cys Lys Ser Lys Arg Leu Arg	
195 200 205	
aaa aat gtg aag cag cat gca gat cag acc gtg aat gaa gac agt gaa	1028
Lys Asn Val Lys Gln His Ala Asp Gln Thr Val Asn Glu Asp Ser Glu	
210 215 220 225	
ggt cgt gac ttg cga caa gtg acc tcg aca aca aag tca tgc agg gag	1076
Gly Arg Asp Leu Arg Gln Val Thr Ser Thr Thr Lys Ser Cys Arg Glu	
230 235 240	
aaa act gaa ctc acc cca gat caa cag act ctt cta cat ttt att atg	1124
Lys Thr Glu Leu Thr Pro Asp Gln Gln Thr Leu Leu His Phe Ile Met	
245 250 255	
gat tca tat aac aaa cag agg atg cct cag gaa ata aca aat aaa att	1172
Asp Ser Tyr Asn Lys Gln Arg Met Pro Gln Glu Ile Thr Asn Lys Ile	

-12-

260						265						270						
tta	aaa	gaa	gaa	ttc	agt	gca	gaa	gaa	aat	ttt	ctc	att	ttg	acg	gaa	1220		
Leu	Lys	Glu	Glu	Phe	Ser	Ala	Glu	Glu	Asn	Phe	Leu	Ile	Leu	Thr	Glu			
	275					280					285							
atg	gca	acc	aat	cat	gta	cag	gtt	ctt	gta	gaa	ttc	aca	aaa	aag	cta	1268		
Met	Ala	Thr	Asn	His	Val	Gln	Val	Leu	Val	Glu	Phe	Thr	Lys	Lys	Leu			
290					295					300					305			
cca	gga	ttt	cag	act	ttg	gac	cat	gaa	gac	cag	att	gct	ttg	ctg	aaa	1316		
Pro	Gly	Phe	Gln	Thr	Leu	Asp	His	Glu	Asp	Gln	Ile	Ala	Leu	Leu	Lys			
				310					315					320				
ggg	tct	gcg	gtt	gaa	gct	atg	ttc	ctt	cgt	tca	gct	gag	att	ttc	aat	1364		
Gly	Ser	Ala	Val	Glu	Ala	Met	Phe	Leu	Arg	Ser	Ala	Glu	Ile	Phe	Asn			
			325					330					335					
aag	aaa	ctt	ccg	tct	ggg	cat	tct	gac	cta	ttg	gaa	gaa	aga	att	cga	1412		
Lys	Lys	Leu	Pro	Ser	Gly	His	Ser	Asp	Leu	Leu	Glu	Glu	Arg	Ile	Arg			
		340					345					350						
aat	agt	ggg	atc	tct	gat	gaa	tat	ata	aca	cct	atg	ttt	agt	ttt	tat	1460		
Asn	Ser	Gly	Ile	Ser	Asp	Glu	Tyr	Ile	Thr	Pro	Met	Phe	Ser	Phe	Tyr			
	355					360					365							
aaa	agt	att	ggg	gaa	ctg	aaa	atg	act	caa	gag	gag	tat	gct	ctg	ctt	1508		
Lys	Ser	Ile	Gly	Glu	Leu	Lys	Met	Thr	Gln	Glu	Glu	Tyr	Ala	Leu	Leu			
370					375					380					385			
aca	gca	att	gtt	atc	ctg	tct	cca	gat	aga	caa	tac	ata	aag	gat	aga	1556		
Thr	Ala	Ile	Val	Ile	Leu	Ser	Pro	Asp	Arg	Gln	Tyr	Ile	Lys	Asp	Arg			
				390					395					400				
gag	gca	gta	gag	aag	ctt	cag	gag	cca	ctt	ctt	gat	gtg	cta	caa	aag	1604		
Glu	Ala	Val	Glu	Lys	Leu	Gln	Glu	Pro	Leu	Leu	Asp	Val	Leu	Gln	Lys			
			405					410					415					
ttg	tgt	aag	att	cac	cag	cct	gaa	aat	cct	caa	cac	ttt	gcc	tgt	ctc	1652		
Leu	Cys	Lys	Ile	His	Gln	Pro	Glu	Asn	Pro	Gln	His	Phe	Ala	Cys	Leu			
		420					425					430						
ctg	ggg	cgc	ctg	act	gaa	tta	cgg	aca	ttc	aat	cat	cac	cac	gct	gag	1700		
Leu	Gly	Arg	Leu	Thr	Glu	Leu	Arg	Thr	Phe	Asn	His	His	His	Ala	Glu			
	435					440					445							
atg	ctg	atg	tca	tgg	aga	gta	aac	gac	cac	aag	ttt	acc	cca	ctt	ctc	1748		
Met	Leu	Met	Ser	Trp	Arg	Val	Asn	Asp	His	Lys	Phe	Thr	Pro	Leu	Leu			
450					455					460					465			
tgt	gaa	atc	tgg	gac	gtg	cag	tga	tgaggattac	aggggagggg	tctagctcct						1802		
Cys	Glu	Ile	Trp	Asp	Val	Gln	*											
				470														

ttttctctct	catattaatc	tgatgtataa	ctttccttta	tttcacttgt	acccagtttc	1862
actcaagaaa	tcttgatgaa	tatttatgtt	gtaattacat	gtgtaacttc	cacaactgta	1922
aatattgggc	tagatagaac	aactttctct	acattgtgtt	ttaaaaggct	ccagggaatc	1982
ctgcattcta	attggcaagc	cctgtttgcc	taattaaatt	gattgttact	tcaattctat	2042
ctgttgaaact	agggaaaatc	tcattttgct	catcttacca	tattgcatat	attttattaa	2102
agagttgtat	tcaatcttgg	caataaagca	aacataatgg	caacagaaaa	aaaaaaaaaa	2162
aaaaaaaaaa	aaaaaaaaaa	aaaaaaaaaa	aaaaaaaaaa	aaaaaaaaaa	aaaaaa	2218

<210> 8
 <211> 472
 <212> PRT
 <213> Homo Sapien

-13-

<400> 8
Met Gly Ser Lys Met Asn Leu Ile Glu His Ser His Leu Pro Thr Thr
1 5 10 15
Asp Glu Phe Ser Phe Ser Glu Asn Leu Phe Gly Val Leu Thr Glu Gln
20 25 30
Val Ala Gly Pro Leu Gly Gln Asn Leu Glu Val Glu Pro Tyr Ser Gln
35 40 45
Tyr Ser Asn Val Gln Phe Pro Gln Val Gln Pro Gln Ile Ser Ser Ser
50 55 60
Ser Tyr Tyr Ser Asn Leu Gly Phe Tyr Pro Gln Gln Pro Glu Glu Trp
65 70 75 80
Tyr Ser Pro Gly Ile Tyr Glu Leu Arg Arg Met Pro Ala Glu Thr Leu
85 90 95
Tyr Gln Gly Glu Thr Glu Val Ala Glu Met Pro Val Thr Lys Lys Pro
100 105 110
Arg Met Gly Ala Ser Ala Gly Arg Ile Lys Gly Asp Glu Leu Cys Val
115 120 125
Val Cys Gly Asp Arg Ala Ser Gly Tyr His Tyr Asn Ala Leu Thr Cys
130 135 140
Glu Gly Cys Lys Gly Phe Phe Arg Arg Ser Ile Thr Lys Asn Ala Val
145 150 155 160
Tyr Lys Cys Lys Asn Gly Gly Asn Cys Val Met Asp Met Tyr Met Arg
165 170 175
Arg Lys Cys Gln Glu Cys Arg Leu Arg Lys Cys Lys Glu Met Gly Met
180 185 190
Leu Ala Glu Cys Leu Leu Thr Glu Ile Gln Cys Lys Ser Lys Arg Leu
195 200 205
Arg Lys Asn Val Lys Gln His Ala Asp Gln Thr Val Asn Glu Asp Ser
210 215 220
Glu Gly Arg Asp Leu Arg Gln Val Thr Ser Thr Thr Lys Ser Cys Arg
225 230 235 240
Glu Lys Thr Glu Leu Thr Pro Asp Gln Gln Thr Leu Leu His Phe Ile
245 250 255
Met Asp Ser Tyr Asn Lys Gln Arg Met Pro Gln Glu Ile Thr Asn Lys
260 265 270
Ile Leu Lys Glu Glu Phe Ser Ala Glu Glu Asn Phe Leu Ile Leu Thr
275 280 285
Glu Met Ala Thr Asn His Val Gln Val Leu Val Glu Phe Thr Lys Lys
290 295 300
Leu Pro Gly Phe Gln Thr Leu Asp His Glu Asp Gln Ile Ala Leu Leu
305 310 315 320
Lys Gly Ser Ala Val Glu Ala Met Phe Leu Arg Ser Ala Glu Ile Phe
325 330 335
Asn Lys Lys Leu Pro Ser Gly His Ser Asp Leu Leu Glu Glu Arg Ile
340 345 350
Arg Asn Ser Gly Ile Ser Asp Glu Tyr Ile Thr Pro Met Phe Ser Phe
355 360 365
Tyr Lys Ser Ile Gly Glu Leu Lys Met Thr Gln Glu Glu Tyr Ala Leu
370 375 380
Leu Thr Ala Ile Val Ile Leu Ser Pro Asp Arg Gln Tyr Ile Lys Asp
385 390 395 400
Arg Glu Ala Val Glu Lys Leu Gln Glu Pro Leu Leu Asp Val Leu Gln
405 410 415
Lys Leu Cys Lys Ile His Gln Pro Glu Asn Pro Gln His Phe Ala Cys
420 425 430
Leu Leu Gly Arg Leu Thr Glu Leu Arg Thr Phe Asn His His His Ala
435 440 445
Glu Met Leu Met Ser Trp Arg Val Asn Asp His Lys Phe Thr Pro Leu
450 455 460
Leu Cys Glu Ile Trp Asp Val Gln
465 470

<210> 9
<211> 5449
<212> DNA
<213> Homo Sapien

-14-

<220>

<221> CDS

<222> (69) ... (1457)

<300>

<308> GeneBank NM_002957

<309> 2002-06-21

<400> 9

```

gcgccggggg ccgcccgcgc ccgcgcgcgc tgcctgcgcc gccggccggg catgagttag 60
tcgcagac atg gac acc aaa cat ttc ctg ccg ctc gat ttc tcc acc cag 110
      Met Asp Thr Lys His Phe Leu Pro Leu Asp Phe Ser Thr Gln
          1              5              10

gtg aac tcc tcc ctc acc tcc ccg acg ggg cga ggc tcc atg gct gcc 158
Val Asn Ser Ser Leu Thr Ser Pro Thr Gly Arg Gly Ser Met Ala Ala
 15              20              25              30

ccc tcg ctg cac ccg tcc ctg ggg cct ggc atc ggc tcc ccg gga cag 206
Pro Ser Leu His Pro Ser Leu Gly Pro Gly Ile Gly Ser Pro Gly Gln
          35              40              45

ctg cat tct ccc atc agc acc ctg agc tcc ccc atc aac ggc atg ggc 254
Leu His Ser Pro Ile Ser Thr Leu Ser Ser Pro Ile Asn Gly Met Gly
          50              55              60

ccg cct ttc tcg gtc atc agc tcc ccc atg ggc ccc cac tcc atg tcg 302
Pro Pro Phe Ser Val Ile Ser Ser Pro Met Gly Pro His Ser Met Ser
          65              70              75

gtg ccc acc aca ccc acc ctg ggc ttc agc act ggc agc ccc cag ctc 350
Val Pro Thr Thr Pro Thr Leu Gly Phe Ser Thr Gly Ser Pro Gln Leu
 80              85              90

agc tca cct atg aac ccc gtc agc agc agc gag gac atc aag ccc ccc 398
Ser Ser Pro Met Asn Pro Val Ser Ser Ser Glu Asp Ile Lys Pro Pro
 95              100              105              110

ctg ggc ctc aat ggc gtc ctc aag gtc ccc gcc cac ccc tca gga aac 446
Leu Gly Leu Asn Gly Val Leu Lys Val Pro Ala His Pro Ser Gly Asn
          115              120              125

atg gct tcc ttc acc aag cac atc tgc gcc atc tgc ggg gac cgc tcc 494
Met Ala Ser Phe Thr Lys His Ile Cys Ala Ile Cys Gly Asp Arg Ser
          130              135              140

tca ggc aag cac tat gga gtg tac agc tgc gag ggg tgc aag ggc ttc 542
Ser Gly Lys His Tyr Gly Val Tyr Ser Cys Glu Gly Cys Lys Gly Phe
          145              150              155

ttc aag cgg acg gtg cgc aag gac ctg acc tac acc tgc cgc gac aac 590
Phe Lys Arg Thr Val Arg Lys Asp Leu Thr Tyr Thr Cys Arg Asp Asn
          160              165              170

aag gac tgc ctg att gac aag cgg cag cgg aac cgg tgc cag tac tgc 638
Lys Asp Cys Leu Ile Asp Lys Arg Gln Arg Asn Arg Cys Gln Tyr Cys
          175              180              185              190

cgc tac cag aag tgc ctg gcc atg ggc atg aag cgg gaa gcc gtg cag 686
Arg Tyr Gln Lys Cys Leu Ala Met Gly Met Lys Arg Glu Ala Val Gln
          195              200              205

gag gag cgg cag cgt ggc aag gac cgg aac gag aat gag gtg gag tcg 734
Glu Glu Arg Gln Arg Gly Lys Asp Arg Asn Glu Asn Glu Val Glu Ser
          210              215              220

acc agc agc gcc aac gag gac atg ccg gtg gag agg atc ctg gag gct 782

```

[illegible]

-16-

```

acccacacggg gcttggggcga ctacaggggtc ttggggcccc agccctggag ctgcaggagt 1807
tgggaacggg gcttttgttt ccgttgctgt ttatcgatgc tggttttcag aattcctgtg 1867
tggccctcct gtctggagtg acatcttcat ctgctctgaa tactgggtgcc cagccagccc 1927
gtgacagctt cccctaatac aggagggggac agctggggggc gcaagctggg gtgtcatcag 1987
caaagacctc agccgcctcg gggatgagag gggactcgtg gggcaagcaa gctgccctgt 2047
gctctgagtg agggggaagg tagcccccctt ttccaaagat aactcacagt tttgccctcg 2107
agccaatgag aacatgagct gccctctgtg caaggtttcg gggccacctc caggctgcag 2167
gggcgggtca ctcaccccccc tgttttctct ctgccttggg gttctgggtt cagactcccg 2227
actccccgtt cagaccagag tgccccgggc cctccccagc ctgagtcttc tccttgcctc 2287
gcggggtggg ctgaggcttg tccttgtttc ctgcagggtt ggccctgggt cgggcagggt 2347
ggggcatcac cacctcactg gccttgctgg aggcacaggg ctctgcggac ctgcagccat 2407
ctgtgaggcc cgcgggggatg ggaggggagg aggggtggcct gttgggtttc ctgagagggg 2467
gcagggtggc tggagagaga ggggctcagg aactgggagc ctctggtggg gggcagatgc 2527
tccgcggcct ggagtggctc tgccgggggca ttggtgggac cctgctcag gccttctctc 2587
tggctgccag ttgtgtctaa aagactcttg gaatctgaga acccggagtc gcagcgccct 2647
cgggcctggg ccacacgcag gccctgggtg gaccaccag cctggtattg tcacggaca 2707
gcgttgttca cccagagcct tacttgggag cctcactgaa cgcctgctct ggttgaagg 2767
ggggtggggg cggggcttgg ggccctcctg gctcagccca gtgcggcctg gcgtcctcc 2827
cgcaggctct gcccccgggc tccggtgggt cggggccctc tcagggtgaa ctgcctctt 2887
ttgcactgga aggcctccc tttggcctga gtacttttcc cgttcacgcc tcagtccct 2947
ggaccagcc tttgtcagtg gcagggtgct gaacagaggg tggatggggg ggataccgga 3007
gggggtcttg tcttcccagc cgcagtctag gaatgatgc ggggggtgga cgccttctcc 3067
atagtcttcc cccacctgga gcaggggcct cctcagtggg gaggggagct gcctacagg 3127
tggaccggga ggcagtggct tggagaggca gcttccagc ctgggtgggg aagaaagtgt 3187
ccattcttct ccttccctgga gctcccagcc agagctgagc ttaggcaccc gagtggagcc 3247
tgcagctgag tctgtgcccg agacaggctg tcagagattc cagaagcctc tcctccccgc 3307
cgccctccac cctgctctt tgagcctcat acctgtacca ggtccccggc cagctggggc 3427
accgtcctga ggcagagtgt actgccagga agccccagct gccctggcg ggtgtgggtg aaatggcagg 3487
cctcccaggg tactcttggg gccccagcgg tgggagtgca aaagacccaa cggcaacacc 3547
aggggtgcagg tgcagccagc gccacccat cctgctcggg acccttggga atgcccgcgg 3607
tggtgccctt ctccagagga aaaagcccag ggacggggcc tccgttgccg ggggtcggct gcttcttggg 3667
aactttgtcg tttccggcgc tggctggctg gctggctgta aagcactgaa gccccccggc 3727
cgccaacccc tgaaagcaga acctggcctc cctggccaca gcagccttac ccaccgctct 3787
acgtgtcccg ggcacttccc gcagccttcc cgtcccttcc tcacggcct tgtagtgtga 3847
cagtgtgttt ggtttgaaaa ggtgatgtgt ggggagtgcg gctcatcact gagtagagag 3907
gtagaatttc tatttaacca gacctgtagt agtattacca atccagttca attaggtga 3967
ttttttgtaa ttattattat tttgggtggga caatctttaa tttctaaag atagcactaa 4027
catcagctca ttagccacct gtgcctgtcc ccgcttggc cggctggat gaagcggctt 4087
ccccgcaggg ccccaacttc ccagtggctg cttcctgggg acccagggca ccccgccacc 4147
ttcaggcacg ctctcagct ggtcacctcc cggttttggc gttcagatgg ggctcctgag 4207
gctcaggagt gaagatgcca cagagccggg ctcccctagg ctgctcggg catgcttggg 4267
agctggcctg ccaggacctt ccaccctggg gcctgtgtca gccgcgggcc ctccgcaccc 4327
tggaagcaca cggcctctgg gaaggacagc cctgaccttc ggttttccga gcacgggtgt 4387
tcccaagaat tctgggctgg cggcctgggt gcagtgtctg agatgacccc gagccccctc 4447
ccgtggggga cccaggaggg ccctgcccga atgtgcagcc tgtgggtagt cggctgggtgt 4507
ccctgtcgtg gagctggggg gcgtgatctg gtgctcgtcc acgcagggtg gtggtgtaaa 4567
catgtatgtg ctgtacagag agacgcgtgt ggagagagcc gcacaccagc gccaccaggg 4627
aaaggcggag cggttaccag tgttttgtgt ttatttttaa tcaagacgtt tcccctgttt 4687
tcctataaat ttgcttcgtg taagcaagta cataaggacc ctcttttggg gaaatccggg 4747
ttcgaatgaa tatctcaagg caggagatgc atctatttta agatgctttg gagcagacag 4807
ctttagccgt tcccaatcct tagcaatgcc ttagctggga cgcatagcta atactttaga 4867
gaggatgaca gatccataaa gagagtaaag ataagagaaa atgtctaaag catctggaaa 4927
ggtaaaaaaa aaaaatctat ttttgtacaa atgtaatttt atccctcatg tatacttggg 4987
tatggcgggg ggagggtgg gactgttttc tttctgcttc tagagattga ggtgaaagct 5047
tcgtccgaga aacgccagga cagacgatgg cagaggagag ggctcctgtg acggcgggca 5107
ggcttgggag gaaaccgcg caatgggggt gtcttccctc ggggcaggag ggtgggcctg 5167
aggctttcaa gggttttctt cccttctcag taatttttaa agccttgcct tgttgtgtcc 5227
tgttgccggc tctggccttc ctgtgactga ctgtgaagtg gcttctccgt acgattgtct 5287
ctgaaacatc gtggcctcag gtgccagggt ttgatggaca gtagcattag aattgtggaa 5347
aaggaacacg caaagggaga agtgtgagag gagaaacaaa atatgagcgt ttaaaataca 5407
tcgccattca gttcgttaaa aaaaaaaaaa aaaaaaaaaa aa 5449

```

<210> 10

<211> 462

<212> PRT

<213> Homo Sapien

-17-

<400> 10

Met	Asp	Thr	Lys	His	Phe	Leu	Pro	Leu	Asp	Phe	Ser	Thr	Gln	Val	Asn
1				5					10					15	
Ser	Ser	Leu	Thr	Ser	Pro	Thr	Gly	Arg	Gly	Ser	Met	Ala	Ala	Pro	Ser
			20					25					30		
Leu	His	Pro	Ser	Leu	Gly	Pro	Gly	Ile	Gly	Ser	Pro	Gly	Gln	Leu	His
		35					40					45			
Ser	Pro	Ile	Ser	Thr	Leu	Ser	Ser	Pro	Ile	Asn	Gly	Met	Gly	Pro	Pro
	50					55					60				
Phe	Ser	Val	Ile	Ser	Ser	Pro	Met	Gly	Pro	His	Ser	Met	Ser	Val	Pro
65					70					75					80
Thr	Thr	Pro	Thr	Leu	Gly	Phe	Ser	Thr	Gly	Ser	Pro	Gln	Leu	Ser	Ser
				85					90					95	
Pro	Met	Asn	Pro	Val	Ser	Ser	Ser	Glu	Asp	Ile	Lys	Pro	Pro	Leu	Gly
			100					105					110		
Leu	Asn	Gly	Val	Leu	Lys	Val	Pro	Ala	His	Pro	Ser	Gly	Asn	Met	Ala
		115					120					125			
Ser	Phe	Thr	Lys	His	Ile	Cys	Ala	Ile	Cys	Gly	Asp	Arg	Ser	Ser	Gly
	130					135					140				
Lys	His	Tyr	Gly	Val	Tyr	Ser	Cys	Glu	Gly	Cys	Lys	Gly	Phe	Phe	Lys
145					150					155					160
Arg	Thr	Val	Arg	Lys	Asp	Leu	Thr	Tyr	Thr	Cys	Arg	Asp	Asn	Lys	Asp
				165				170						175	
Cys	Leu	Ile	Asp	Lys	Arg	Gln	Arg	Asn	Arg	Cys	Gln	Tyr	Cys	Arg	Tyr
			180					185					190		
Gln	Lys	Cys	Leu	Ala	Met	Gly	Met	Lys	Arg	Glu	Ala	Val	Gln	Glu	Glu
		195					200					205			
Arg	Gln	Arg	Gly	Lys	Asp	Arg	Asn	Glu	Asn	Glu	Val	Glu	Ser	Thr	Ser
	210				215						220				
Ser	Ala	Asn	Glu	Asp	Met	Pro	Val	Glu	Arg	Ile	Leu	Glu	Ala	Glu	Leu
225					230					235					240
Ala	Val	Glu	Pro	Lys	Thr	Glu	Thr	Tyr	Val	Glu	Ala	Asn	Met	Gly	Leu
				245				250						255	
Asn	Pro	Ser	Ser	Pro	Asn	Asp	Pro	Val	Thr	Asn	Ile	Cys	Gln	Ala	Ala
			260					265					270		
Asp	Lys	Gln	Leu	Phe	Thr	Leu	Val	Glu	Trp	Ala	Lys	Arg	Ile	Pro	His
		275					280					285			
Phe	Ser	Glu	Leu	Pro	Leu	Asp	Asp	Gln	Val	Ile	Leu	Leu	Arg	Ala	Gly
	290					295					300				
Trp	Asn	Glu	Leu	Leu	Ile	Ala	Ser	Phe	Ser	His	Arg	Ser	Ile	Ala	Val
305					310					315					320
Lys	Asp	Gly	Ile	Leu	Leu	Ala	Thr	Gly	Leu	His	Val	His	Arg	Asn	Ser
				325					330					335	
Ala	His	Ser	Ala	Gly	Val	Gly	Ala	Ile	Phe	Asp	Arg	Val	Leu	Thr	Glu
			340					345					350		
Leu	Val	Ser	Lys	Met	Arg	Asp	Met	Gln	Met	Asp	Lys	Thr	Glu	Leu	Gly
		355					360					365			
Cys	Leu	Arg	Ala	Ile	Val	Leu	Phe	Asn	Pro	Asp	Ser	Lys	Gly	Leu	Ser
	370					375					380				
Asn	Pro	Ala	Glu	Val	Glu	Ala	Leu	Arg	Glu	Lys	Val	Tyr	Ala	Ser	Leu
385					390					395					400
Glu	Ala	Tyr	Cys	Lys	His	Lys	Tyr	Pro	Glu	Gln	Pro	Gly	Arg	Phe	Ala
				405					410					415	
Lys	Leu	Leu	Leu	Arg	Leu	Pro	Ala	Leu	Arg	Ser	Ile	Gly	Leu	Lys	Cys
			420					425					430		
Leu	Glu	His	Leu	Phe	Phe	Phe	Lys	Leu	Ile	Gly	Asp	Thr	Pro	Ile	Asp
		435					440					445			
Thr	Phe	Leu	Met	Glu	Met	Leu	Glu	Ala	Pro	His	Gln	Met	Thr		
	450					455						460			

<210> 11

<211> 2081

<212> DNA

<213> Mus musculus

<220>

- 18 -

<221> CDS

<222> (167) ... (1573)

<300>

<308> GeneBank X57638

<309> 1991-03-19

<400> 11

```

gtcacagcct aggcctttgct ggggacctga gaaacgctgc cgccaagttg aagttcaagg 60
ccctgccttc cctgtgaact gacgtttgtg gctgggtcaag ttcgggaaca agacgttgtc 120
atcacagctt agcgctctgt ggctgcctg gccacatcca tccaac atg gtg gac 175
                                     Met Val Asp
                                     1

aca gag agc ccc atc tgt cct ctc tcc cca ctg gag gca gat gac ctg 223
Thr Glu Ser Pro Ile Cys Pro Leu Ser Pro Leu Glu Ala Asp Asp Leu
      5                10                15

gaa agt ccc tta tct gaa gaa ttc tta caa gaa atg gga aac att caa 271
Glu Ser Pro Leu Ser Glu Glu Phe Leu Gln Glu Met Gly Asn Ile Gln
      20                25                30                35

gag att tct cag tcc atc ggt gag gag agc tct gga agc ttt ggt ttt 319
Glu Ile Ser Gln Ser Ile Gly Glu Glu Ser Ser Gly Ser Phe Gly Phe
                        40                45                50

gca gac tac cag tac tta gga agc tgt ccg ggc tcc gag ggc tct gtc 367
Ala Asp Tyr Gln Tyr Leu Gly Ser Cys Pro Gly Ser Glu Gly Ser Val
                        55                60                65

atc aca gac acc ctc tct cca cgt tcc agc cct tcc tca gtc agc tgc 415
Ile Thr Asp Thr Leu Ser Pro Arg Ser Ser Pro Ser Ser Val Ser Cys
                        70                75                80

ccc gtg atc ccc gcc agc acg gac gag tcc ccc ggc agt gcc ctg aac 463
Pro Val Ile Pro Ala Ser Thr Asp Glu Ser Pro Gly Ser Ala Leu Asn
                        85                90                95

atc gag tgt cga ata tgt ggg gac aag gcc tca ggg tac cac tac gga 511
Ile Glu Cys Arg Ile Cys Gly Asp Lys Ala Ser Gly Tyr His Tyr Gly
      100                105                110                115

gtt cac gca tgt gaa ggc tgt aag ggc ttc ttt cgg cga act att cgg 559
Val His Ala Cys Glu Gly Cys Lys Gly Phe Phe Arg Arg Thr Ile Arg
                        120                125                130

ctg aag ctg gtg tac gac aag tgt gat cgg agc tgc aag att cag aag 607
Leu Lys Leu Val Tyr Asp Lys Cys Asp Arg Ser Cys Lys Ile Gln Lys
                        135                140                145

aag aac cgg aac aaa tgc cag tac tgc cgt ttt cac aag tgc ctg tct 655
Lys Asn Arg Asn Lys Cys Gln Tyr Cys Arg Phe His Lys Cys Leu Ser
                        150                155                160

gtc ggg atg tca cac aat gca att cgc ttt gga aga atg cca aga tct 703
Val Gly Met Ser His Asn Ala Ile Arg Phe Gly Arg Met Pro Arg Ser
                        165                170                175

gaa aaa gca aaa ctg aaa gca gaa att ctt acc tgt gaa cac gac ctg 751
Glu Lys Ala Lys Leu Lys Ala Glu Ile Leu Thr Cys Glu His Asp Leu
      180                185                190                195

aaa gat tcg gaa act gca gac ctc aaa tct ctg ggc aag aga atc cac 799
Lys Asp Ser Glu Thr Ala Asp Leu Lys Ser Leu Gly Lys Arg Ile His
                        200                205                210

gaa gcc tac ctg aag aac ttc aac atg aac aag gtc aag gcc cgg gtc 847

```


-19-

Glu 215	Ala 220	Tyr 225	Leu 230	Lys 235	Asn 240	Phe 245	Asn 250	Met 255	Asn 260	Lys 265	Val 270	Lys 275	Ala 280	Arg 285	Val 290	
ata Ile	ctc Leu	gcg Ala 230	gga Gly	aag Lys	acc Thr	agc Ser	aac Asn 235	aac Asn	ccg Pro	cct Pro	ttt Phe	gtc Val 240	ata Ile	cat His	gac Asp	895
atg Met	gag Glu 245	acc Thr	ttg Leu	tgt Cys	atg Met	gcc Ala 250	gag Glu	aag Lys	acg Thr	ctt Leu	gtg Val 255	gcc Ala	aag Lys	atg Met	gtg Val	943
gcc Ala 260	aac Asn	ggc Gly	gtc Val	gaa Glu	gac Asp 265	aaa Lys	gag Glu	gca Ala	gag Glu	gtc Val 270	cga Arg	ttc Phe	ttc Phe	cac His	tgc Cys 275	991
tgc Cys	cag Gln	tgc Cys	atg Met	tcc Ser 280	gtg Val	gag Glu	acc Thr	gtc Val	acg Thr 285	gag Glu	ctc Leu	aca Thr	gaa Glu	ttt Phe 290	gcc Ala	1039
aag Lys	gct Ala	atc Ile	cca Pro 295	ggc Gly	ttt Phe	gca Ala	aac Asn	ttg Leu 300	gac Asp	ttg Leu	aac Asn	gac Asp	caa Gln 305	gtc Val	acc Thr	1087
ttg Leu	cta Leu	aag Lys 310	tac Tyr	ggt Gly	gtg Val	tat Tyr	gaa Glu 315	gcc Ala	atc Ile	ttc Phe	acg Thr	atg Met 320	ctg Leu	tcc Ser	tcc Ser	1135
ttg Leu	atg Met 325	aac Asn	aaa Lys	gac Asp	ggg Gly	atg Met 330	ctg Leu	atc Ile	gcg Ala	tac Tyr	ggc Gly 335	aat Asn	ggc Gly	ttt Phe	atc Ile	1183
aca Thr 340	cgc Arg	gag Glu	ttc Phe	ctt Leu	aag Lys 345	aac Asn	ctg Leu	agg Arg	aag Lys	ccg Pro 350	ttc Phe	tgt Cys	gac Asp	atc Ile	atg Met 355	1231
gaa Glu	ccc Pro	aag Lys	ttt Phe	gac Asp 360	ttc Phe	gct Ala	atg Met	aag Lys	ttc Phe 365	aat Asn	gcc Ala	tta Leu	gaa Glu	ctg Leu 370	gat Asp	1279
gac Asp	agt Ser	gac Asp	att Ile 375	tcc Ser	ctg Leu	ttt Phe	gtg Val	gct Ala 380	gct Ala	ata Ile	att Ile	tgc Cys	tgt Cys 385	gga Gly	gat Asp	1327
cgg Arg	cct Pro	ggc Gly 390	ctt Leu	cta Leu	aac Asn	ata Ile	ggc Gly 395	tac Tyr	att Ile	gag Glu	aag Lys	ttg Leu 400	cag Gln	gag Glu	ggg Gly	1375
att Ile	gtg Val 405	cac His	gtg Val	ctt Leu	aag Lys	ctc Leu 410	cac His	ctg Leu	cag Gln	agc Ser	aac Asn 415	cat His	cca Pro	gat Asp	gac Asp	1423
acc Thr 420	ttc Phe	ctc Leu	ttc Phe	cca Pro	aag Lys 425	ctc Leu	ctt Leu	caa Gln	aaa Lys	atg Met 430	gtg Val	gac Asp	ctt Leu	cgg Arg	cag Gln 435	1471
ctg Leu	gtc Val	acg Thr	gag Glu	cat His 440	gcg Ala	cag Gln	ctc Leu	gta Val	cag Gln 445	gtc Val	atc Ile	aag Lys	aag Lys	acc Thr 450	gag Glu	1519
tcc Ser	gac Asp	gca Ala	gcg Ala	ctg Leu	cac His	cca Pro	ctg Leu	ttg Leu 460	caa Gln	gag Glu	atc Ile	tac Tyr	aga Arg 465	gac Asp	atg Met	1567
tac Tyr	tga *	tctttt	cctga	gatggc	caggc	cattacc	act	gttcagg	ggac	ctccgagg	gcc					1623

-20-

```

tgcggcccca tacaggagag cagggatttg cacagagggc ctccctccta cgcttgggga 1683
tgaagagggc tgagcgtagg taatgcgggc tctccccaca tcctttctga atgggcactt 1743
ctaagactac ctgctaccga aatgggggtg atcggaggct aataggattc agacagtgac 1803
agacaacggc agtccccagt ctggtcttaa cgggcccaat gttaatcaat gcacagcact 1863
ctacgttgcg ttataaattc gccattaatt aacgggtaac ctcgaagtct gagcgggtctg 1923
ttcccttcct gccacccttc tggctatgtg cactctctta aatccctgaa aactaatctg 1983
cactttttta cctttgaaaa cctacaagtc aaggtgtggc ccaaggttag ccatttaa 2043
gtggcaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaa

```

<210> 12

<211> 468

<212> PRT

<213> Mus musculus

<400> 12

```

Met Val Asp Thr Glu Ser Pro Ile Cys Pro Leu Ser Pro Leu Glu Ala
1      5      10     15
Asp Asp Leu Glu Ser Pro Leu Ser Glu Glu Phe Leu Gln Glu Met Gly
20     25     30
Asn Ile Gln Glu Ile Ser Gln Ser Ile Gly Glu Glu Ser Ser Gly Ser
35     40     45
Phe Gly Phe Ala Asp Tyr Gln Tyr Leu Gly Ser Cys Pro Gly Ser Glu
50     55     60
Gly Ser Val Ile Thr Asp Thr Leu Ser Pro Arg Ser Ser Pro Ser Ser
65     70     75     80
Val Ser Cys Pro Val Ile Pro Ala Ser Thr Asp Glu Ser Pro Gly Ser
85     90     95
Ala Leu Asn Ile Glu Cys Arg Ile Cys Gly Asp Lys Ala Ser Gly Tyr
100    105    110
His Tyr Gly Val His Ala Cys Glu Gly Cys Lys Gly Phe Phe Arg Arg
115    120    125
Thr Ile Arg Leu Lys Leu Val Tyr Asp Lys Cys Asp Arg Ser Cys Lys
130    135    140
Ile Gln Lys Lys Asn Arg Asn Lys Cys Gln Tyr Cys Arg Phe His Lys
145    150    155    160
Cys Leu Ser Val Gly Met Ser His Asn Ala Ile Arg Phe Gly Arg Met
165    170    175
Pro Arg Ser Glu Lys Ala Lys Leu Lys Ala Glu Ile Leu Thr Cys Glu
180    185    190
His Asp Leu Lys Asp Ser Glu Thr Ala Asp Leu Lys Ser Leu Gly Lys
195    200    205
Arg Ile His Glu Ala Tyr Leu Lys Asn Phe Asn Met Asn Lys Val Lys
210    215    220
Ala Arg Val Ile Leu Ala Gly Lys Thr Ser Asn Asn Pro Pro Phe Val
225    230    235    240
Ile His Asp Met Glu Thr Leu Cys Met Ala Glu Lys Thr Leu Val Ala
245    250    255
Lys Met Val Ala Asn Gly Val Glu Asp Lys Glu Ala Glu Val Arg Phe
260    265    270
Phe His Cys Cys Gln Cys Met Ser Val Glu Thr Val Thr Glu Leu Thr
275    280    285
Glu Phe Ala Lys Ala Ile Pro Gly Phe Ala Asn Leu Asp Leu Asn Asp
290    295    300
Gln Val Thr Leu Leu Lys Tyr Gly Val Tyr Glu Ala Ile Phe Thr Met
305    310    315    320
Leu Ser Ser Leu Met Asn Lys Asp Gly Met Leu Ile Ala Tyr Gly Asn
325    330    335
Gly Phe Ile Thr Arg Glu Phe Leu Lys Asn Leu Arg Lys Pro Phe Cys
340    345    350
Asp Ile Met Glu Pro Lys Phe Asp Phe Ala Met Lys Phe Asn Ala Leu
355    360    365
Glu Leu Asp Asp Ser Asp Ile Ser Leu Phe Val Ala Ala Ile Ile Cys
370    375    380
Cys Gly Asp Arg Pro Gly Leu Leu Asn Ile Gly Tyr Ile Glu Lys Leu
385    390    395    400
Gln Glu Gly Ile Val His Val Leu Lys Leu His Leu Gln Ser Asn His
405    410    415

```

-21-

[illegible]

```
<210> 13
<211> 1323
<212> DNA
<213> Mus musculus
```

```
<220>
<221> CDS
<222> (1) ... (1323)
```

<300>
<308> GeneBank U10375
<309> 1994-07-22

<400> 13

atg Met 1	gaa Glu	cag Gln	cca Pro	cag Gln 5	gag Glu	gag Glu	acc Thr	cct Pro	gag Glu 10	gcc Ala	cgg Arg	gaa Glu	gag Glu	gag Glu 15	aaa Lys	48
gag Glu	gaa Glu	gtg Val	gcc Ala 20	atg Met	ggg Gly	gac Asp	gga Gly	gcc Ala 25	ccg Pro	gag Glu	ctc Leu	aat Asn	ggg Gly 30	gga Gly	cca Pro	96
gaa Glu	cac His	acg Thr 35	ctt Leu	cct Pro	tcc Ser	agc Ser	agc Ser 40	tgt Cys	gca Ala	gac Asp	ctc Leu	tcc Ser 45	cag Gln	aat Asn	tcc Ser	144
tcc Ser	cct Pro 50	tcc Ser	tcc Ser	ctg Leu	ctg Leu	gac Asp 55	cag Gln	ctg Leu	cag Gln	atg Met	ggc Gly 60	tgt Cys	gat Asp	ggg Gly	gcc Ala	192
tca Ser 65	ggc Gly	ggc Gly	agc Ser	ctc Leu	aac Asn 70	atg Met	gaa Glu	tgt Cys	cgg Arg	gtg Val 75	tgc Cys	ggg Gly	gac Asp	aag Lys	gcc Ala 80	240
tcg Ser	ggc Gly	ttc Phe	cac His	tac Tyr 85	ggg Gly	gtc Val	cac His	gcg Ala	tgc Cys 90	gag Glu	ggg Gly	tgc Cys	aag Lys	ggc Gly 95	ttc Phe	288
ttc Phe	cgc Arg	cgg Arg	aca Thr 100	atc Ile	cgc Arg	atg Met	aag Lys	ctc Leu 105	gag Glu	tat Tyr	gag Glu	aag Lys	tgc Cys 110	gat Asp	cgg Arg	336
atc Ile	tgc Cys	aag Lys 115	atc Ile	cag Gln	aag Lys	aag Lys	aac Asn 120	cgc Arg	aac Asn	aag Lys	tgt Cys	cag Gln 125	tac Tyr	tgc Cys	cgc Arg	384
ttc Phe	cag Gln 130	aag Lys	tgc Cys	ctg Leu	gca Ala	ctc Leu 135	ggc Gly	atg Met	tcg Ser	cac His	aac Asn 140	gct Ala	atc Ile	cgc Arg	ttt Phe	432
gga Gly 145	cgg Arg	atg Met	ccg Pro	gac Asp	ggc Gly 150	gag Glu	aag Lys	agg Arg	aag Lys	ctg Leu 155	gtg Val	gcg Ala	ggg Gly	ctg Leu	act Thr 160	480
gcc Ala	agc Ser	gag Glu	ggg Gly	tgc Cys 165	cag Gln	cac His	aac Asn	ccc Pro	cag Gln 170	ctg Leu	gcc Ala	gac Asp	ctg Leu	aag Lys 175	gcc Ala	528

-22-

ttc tct aag cac atc tac aac gcc tac ctg aaa aac ttc aac atg acc	576
Phe Ser Lys His Ile Tyr Asn Ala Tyr Leu Lys Asn Phe Asn Met Thr	
180 185 190	
aaa aag aag gcc cgg agc atc ctc acc ggc aag tcc agc cac aac gca	624
Lys Lys Lys Ala Arg Ser Ile Leu Thr Gly Lys Ser Ser His Asn Ala	
195 200 205	
ccc ttt gtc atc cac gac atc gag aca ctg tgg cag gca gag aag ggc	672
Pro Phe Val Ile His Asp Ile Glu Thr Leu Trp Gln Ala Glu Lys Gly	
210 215 220	
ctg gtg tgg aaa cag ctg gtg aac ggg ctg ccg ccc tac aac gag atc	720
Leu Val Trp Lys Gln Leu Val Asn Gly Leu Pro Pro Tyr Asn Glu Ile	
225 230 235 240	
agt gtg cac gtg ttc tac cgc tgc cag tcc acc aca gtg gag aca gtc	768
Ser Val His Val Phe Tyr Arg Cys Gln Ser Thr Thr Val Glu Thr Val	
245 250 255	
cga gag ctc acc gag ttc gcc aag aac atc ccc aac ttc agc agc ctc	816
Arg Glu Leu Thr Glu Phe Ala Lys Asn Ile Pro Asn Phe Ser Ser Leu	
260 265 270	
ttc ctc aat gac cag gtg acc ctc ctc aag tat ggc gtg cac gag gcc	864
Phe Leu Asn Asp Gln Val Thr Leu Leu Lys Tyr Gly Val His Glu Ala	
275 280 285	
atc ttt gcc atg ctg gcc tcc atc gtc aac aaa gac ggg ctg ctg gtg	912
Ile Phe Ala Met Leu Ala Ser Ile Val Asn Lys Asp Gly Leu Leu Val	
290 295 300	
gcc aac ggc agt ggc ttc gtc acc cac gag ttc ttg cga agt ctc cgc	960
Ala Asn Gly Ser Gly Phe Val Thr His Glu Phe Leu Arg Ser Leu Arg	
305 310 315 320	
aag ccc ttc agt gac atc att gag ccc aag ttc gag ttt gct gtc aag	1008
Lys Pro Phe Ser Asp Ile Ile Glu Pro Lys Phe Glu Phe Ala Val Lys	
325 330 335	
ttc aat gcg ctg gag ctc gat gac agt gag ctg gcg ctc ttc atc gcg	1056
Phe Asn Ala Leu Glu Leu Asp Asp Ser Asp Leu Ala Leu Phe Ile Ala	
340 345 350	
gcc atc att ctg tgt gga gac cgg cca ggc ctc atg aat gtg ccc cag	1104
Ala Ile Ile Leu Cys Gly Asp Arg Pro Gly Leu Met Asn Val Pro Gln	
355 360 365	
gta gaa gcc atc cag gac acc att ctg cgg gct cta gaa ttc cat ctg	1152
Val Glu Ala Ile Gln Asp Thr Ile Leu Arg Ala Leu Glu Phe His Leu	
370 375 380	
cag gtc aac cac cct gac agc cag tac ctc ttc ccc aag ctg ctg cag	1200
Gln Val Asn His Pro Asp Ser Gln Tyr Leu Phe Pro Lys Leu Leu Gln	
385 390 395 400	
aag atg gca gac ctg cgg cag ctg gtc act gag cat gcc cag atg atg	1248
Lys Met Ala Asp Leu Arg Gln Leu Val Thr Glu His Ala Gln Met Met	
405 410 415	
cag tgg cta aag aag acg gag agt gag acc ttg ctg cac ccc ctg ctc	1296
Gln Trp Leu Lys Lys Thr Glu Ser Glu Thr Leu Leu His Pro Leu Leu	
420 425 430	
cag gaa atc tac aag gac atg tac taa	1323
Gln Glu Ile Tyr Lys Asp Met Tyr *	

-23-

435

440

<210> 14
 <211> 440
 <212> PRT
 <213> Mus musculus

<400> 14

Met	Glu	Gln	Pro	Gln	Glu	Glu	Thr	Pro	Glu	Ala	Arg	Glu	Glu	Glu	Lys
1				5					10					15	
Glu	Glu	Val	Ala	Met	Gly	Asp	Gly	Ala	Pro	Glu	Leu	Asn	Gly	Gly	Pro
			20					25					30		
Glu	His	Thr	Leu	Pro	Ser	Ser	Ser	Cys	Ala	Asp	Leu	Ser	Gln	Asn	Ser
		35					40					45			
Ser	Pro	Ser	Ser	Leu	Leu	Asp	Gln	Leu	Gln	Met	Gly	Cys	Asp	Gly	Ala
	50					55					60				
Ser	Gly	Gly	Ser	Leu	Asn	Met	Glu	Cys	Arg	Val	Cys	Gly	Asp	Lys	Ala
65					70				75						80
Ser	Gly	Phe	His	Tyr	Gly	Val	His	Ala	Cys	Glu	Gly	Cys	Lys	Gly	Phe
			85					90						95	
Phe	Arg	Arg	Thr	Ile	Arg	Met	Lys	Leu	Glu	Tyr	Glu	Lys	Cys	Asp	Arg
			100					105						110	
Ile	Cys	Lys	Ile	Gln	Lys	Lys	Asn	Arg	Asn	Lys	Cys	Gln	Tyr	Cys	Arg
		115					120					125			
Phe	Gln	Lys	Cys	Leu	Ala	Leu	Gly	Met	Ser	His	Asn	Ala	Ile	Arg	Phe
	130					135					140				
Gly	Arg	Met	Pro	Asp	Gly	Glu	Lys	Arg	Lys	Leu	Val	Ala	Gly	Leu	Thr
145					150					155					160
Ala	Ser	Glu	Gly	Cys	Gln	His	Asn	Pro	Gln	Leu	Ala	Asp	Leu	Lys	Ala
				165				170						175	
Phe	Ser	Lys	His	Ile	Tyr	Asn	Ala	Tyr	Leu	Lys	Asn	Phe	Asn	Met	Thr
			180					185					190		
Lys	Lys	Lys	Ala	Arg	Ser	Ile	Leu	Thr	Gly	Lys	Ser	Ser	His	Asn	Ala
		195					200					205			
Pro	Phe	Val	Ile	His	Asp	Ile	Glu	Thr	Leu	Trp	Gln	Ala	Glu	Lys	Gly
	210					215					220				
Leu	Val	Trp	Lys	Gln	Leu	Val	Asn	Gly	Leu	Pro	Pro	Tyr	Asn	Glu	Ile
225					230					235					240
Ser	Val	His	Val	Phe	Tyr	Arg	Cys	Gln	Ser	Thr	Thr	Val	Glu	Thr	Val
				245					250					255	
Arg	Glu	Leu	Thr	Glu	Phe	Ala	Lys	Asn	Ile	Pro	Asn	Phe	Ser	Ser	Leu
			260					265					270		
Phe	Leu	Asn	Asp	Gln	Val	Thr	Leu	Lys	Tyr	Gly	Val	His	Glu	Ala	
		275					280				285				
Ile	Phe	Ala	Met	Leu	Ala	Ser	Ile	Val	Asn	Lys	Asp	Gly	Leu	Leu	Val
	290					295					300				
Ala	Asn	Gly	Ser	Gly	Phe	Val	Thr	His	Glu	Phe	Leu	Arg	Ser	Leu	Arg
305					310					315					320
Lys	Pro	Phe	Ser	Asp	Ile	Ile	Glu	Pro	Lys	Phe	Glu	Phe	Ala	Val	Lys
				325					330					335	
Phe	Asn	Ala	Leu	Glu	Leu	Asp	Asp	Ser	Asp	Leu	Ala	Leu	Phe	Ile	Ala
			340					345					350		
Ala	Ile	Ile	Leu	Cys	Gly	Asp	Arg	Pro	Gly	Leu	Met	Asn	Val	Pro	Gln
		355					360						365		
Val	Glu	Ala	Ile	Gln	Asp	Thr	Ile	Leu	Arg	Ala	Leu	Glu	Phe	His	Leu
	370					375					380				
Gln	Val	Asn	His	Pro	Asp	Ser	Gln	Tyr	Leu	Phe	Pro	Lys	Leu	Leu	Gln
385					390					395					400
Lys	Met	Ala	Asp	Leu	Arg	Gln	Leu	Val	Thr	Glu	His	Ala	Gln	Met	Met
				405					410					415	
Gln	Trp	Leu	Lys	Thr	Glu	Ser	Glu	Thr	Leu	Leu	His	Pro	Leu	Leu	
			420				425						430		
Gln	Glu	Ile	Tyr	Lys	Asp	Met	Tyr								
		435					440								

- 24 -

<210> 15
 <211> 1827
 <212> DNA
 <213> Homo Sapien

<220>
 <221> CDS
 <222> (292) ... (1683)

<300>
 <308> GeneBank XM_053680
 <309> 2002-05-08

<400> 15
 gtagcgggtga cggcggcggc ggcggcggcg gcagcattat gcgtgattac tgacaggcac 60
 cagctgctgc cgccacagcc gtctcaaacg cactatgtgg actctccgat ctagaggcag 120
 attcctgact aatcccagag ggctggccca gcctgtgctc cccgggctgc taggaagcga 180
 tgaccactct tgttagccca agttgaagaa agccgggctg tgcctgggag ccgagagagg 240
 cggtaatatatt tagaagctgc acaggagagg aacatgaact gacgagtaaa c atg tat 297
 Met Tyr
 1

gga aat tat tct cac ttc atg aag ttt ccc gca ggc tat gga ggc tcc 345
 Gly Asn Tyr Ser His Phe Met Lys Phe Pro Ala Gly Tyr Gly Gly Ser
 5 10 15

cct ggc cac act ggc tct aca tcc atg agc cca tca gca gcc ttg tcc 393
 Pro Gly His Thr Gly Ser Thr Ser Met Ser Pro Ser Ala Ala Leu Ser
 20 25 30

aca ggg aag cca atg gac agc cac ccc agc tac aca gat acc cca gtg 441
 Thr Gly Lys Pro Met Asp Ser His Pro Ser Tyr Thr Asp Thr Pro Val
 35 40 45 50

agt gcc cca cgg act ctg agt gca gtg ggg acc ccc ctc aat gcc ctg 489
 Ser Ala Pro Arg Thr Leu Ser Ala Val Gly Thr Pro Leu Asn Ala Leu
 55 60 65

ggc tct cca tat cga gtc atc acc tct gcc atg ggc cca ccc tca gga 537
 Gly Ser Pro Tyr Arg Val Ile Thr Ser Ala Met Gly Pro Pro Ser Gly
 70 75 80

gca ctt gca gcg cct cca gga atc aac ttg gtt gcc cca ccc agc tct 585
 Ala Leu Ala Ala Pro Pro Gly Ile Asn Leu Val Ala Pro Pro Ser Ser
 85 90 95

cag cta aat gtg gtc aac agt gtc agc agt tca gag gac atc aag ccc 633
 Gln Leu Asn Val Val Asn Ser Val Ser Ser Ser Glu Asp Ile Lys Pro
 100 105 110

tta cca ggg ctt ccc ggg att gga aac atg aac tac cca tcc acc agc 681
 Leu Pro Gly Leu Pro Gly Ile Gly Asn Met Asn Tyr Pro Ser Thr Ser
 115 120 125 130

ccc gga tct ctg gtt aaa cac atc tgt gcc atc tgt gga gac aga tcc 729
 Pro Gly Ser Leu Val Lys His Ile Cys Ala Ile Cys Gly Asp Arg Ser
 135 140 145

tca gga aag cac tac ggg gta tac agt tgt gaa ggc tgc aaa ggg ttc 777
 Ser Gly Lys His Tyr Gly Val Tyr Ser Cys Glu Gly Cys Lys Gly Phe
 150 155 160

ttc aag agg acg ata agg aag gac ctc atc tac acg tgt cgg gat aat 825
 Phe Lys Arg Thr Ile Arg Lys Asp Leu Ile Tyr Thr Cys Arg Asp Asn
 165 170 175

aaa gac tgc ctc att gac aag cgt cag cgc aac cgc tgc cag tac tgt 873

-25-

Lys 180	Asp	Cys	Leu	Ile	Asp	Lys 185	Arg	Gln	Arg	Asn	Arg 190	Cys	Gln	Tyr	Cys	
cgc Arg 195	tat Tyr	cag Gln	aag Lys	tgc Cys	ctt Leu 200	gtc Val	atg Met	ggc Gly	atg Met	aag Lys 205	agg Arg	gaa Glu	gct Ala	gtg Val	caa Gln 210	921
gaa Glu	gaa Glu	aga Arg	cag Gln	agg Arg 215	agc Ser	cga Arg	gag Glu	cga Arg	gct Ala 220	gag Glu	agt Ser	gag Glu	gca Ala	gaa Glu 225	tgt Cys	969
gct Ala	acc Thr	agt Ser	ggt Gly 230	cat His	gaa Glu	gac Asp	atg Met	cct Pro 235	gtg Val	gag Glu	agg Arg	att Ile	cta Leu 240	gaa Glu	gct Ala	1017
gaa Glu	ctt Leu	gct Ala 245	gtt Val	gaa Glu	cca Pro	aag Lys	aca Thr 250	gaa Glu	tcc Ser	tat Tyr	ggt Gly	gac Asp 255	atg Met	aat Asn	atg Met	1065
gag Glu	aac Asn 260	tcg Ser	aca Thr	aat Asn	gac Asp	cct Pro 265	gtt Val	acc Thr	aac Asn	ata Ile	tgt Cys 270	cat His	gct Ala	gct Ala	gac Asp	1113
aag Lys 275	cag Gln	ctt Leu	ttc Phe	acc Thr	ctc Leu 280	gtt Val	gaa Glu	tgg Trp	gcc Ala	aag Lys 285	cgt Arg	att Ile	ccc Pro	cac His	ttc Phe 290	1161
tct Ser	gac Asp	ctc Leu	acc Thr	ttg Leu 295	gag Glu	gac Asp	cag Gln	gtc Val	att Ile 300	ttg Leu	ctt Leu	cgg Arg	gca Ala	ggg Gly 305	tgg Trp	1209
aat Asn	gaa Glu	ttg Leu	ctg Leu	att Ile	gcc Ala	tct Ser	ttc Phe	tcc Ser 315	cac His	cgc Arg	tca Ser	ggt Val	tcc Ser 320	gtg Val	cag Gln	1257
gat Asp	ggc Gly	atc Ile 325	ctt Leu	ctg Leu	gcc Ala	acg Thr	ggt Gly 330	tta Leu	cat His	gtc Val	cac His	cgg Arg 335	agc Ser	agt Ser	gcc Ala	1305
cac His 340	agt Ser	gct Ala	ggg Gly	gtc Val	ggc Gly	tcc Ser 345	atc Ile	ttt Phe	gac Asp	aga Arg	gtc Val 350	cta Leu	act Thr	gag Glu	ctg Leu	1353
gtt Val 355	tcc Ser	aaa Lys	atg Met	aaa Lys	gac Asp 360	atg Met	cag Gln	atg Met	gac Asp	aag Lys 365	tcg Ser	gaa Glu	ctg Leu	gga Gly	tgc Cys 370	1401
ctg Leu	cga Arg	gcc Ala	att Ile	gta Val 375	ctc Leu	ttt Phe	aac Asn	cca Pro	gat Asp 380	gcc Ala	aag Lys	ggc Gly	ctg Leu	tcc Ser 385	aac Asn	1449
ccc Pro	tct Ser	gag Glu	gtg Val 390	gag Glu	act Thr	ctg Leu	cga Arg	gag Glu 395	aag Lys	gtt Val	tat Tyr	gcc Ala	acc Thr 400	ctt Leu	gag Glu	1497
gcc Ala	tac Tyr	acc Thr 405	aag Lys	cag Gln	aag Lys	tat Tyr	ccg Pro 410	gaa Glu	cag Gln	cca Pro	ggc Gly 415	agg Arg	ttt Phe	gcc Ala	aag Lys	1545
ctg Leu 420	ctg Leu	ctg Leu	cgc Arg	ctc Leu	cca Pro	gct Ala 425	ctg Leu	cgt Arg	tcc Ser	att Ile	ggc Gly 430	ttg Leu	aaa Lys	tgc Cys	ctg Leu	1593
gag Glu 435	cac His	ctc Leu	ttc Phe	ttc Phe	ttc Phe 440	aag Lys	ctc Leu	atc Ile	ggg Gly	gac Asp 445	acc Thr	ccc Pro	att Ile	gac Asp	acc Thr 450	1641

-26-

ttc ctc atg gag atg ttg gag acc ccg ctg cag atc acc tga 1683
 Phe Leu Met Glu Met Leu Glu Thr Pro Leu Gln Ile Thr *
 455 460

gccccaccag ccacagcctc cccacccagg atgacccttg ggcaggtgtg tgtggacccc 1743
 caccctgcac tttcctccac ctcccaccct gaccccttc ctgtcccca aatgtgatgc 1803
 ttataataaa gaaaaccttt ctac 1827

<210> 16
 <211> 463
 <212> PRT
 <213> Homo Sapien

<400> 16
 Met Tyr Gly Asn Tyr Ser His Phe Met Lys Phe Pro Ala Gly Tyr Gly
 1 5 10 15
 Gly Ser Pro Gly His Thr Gly Ser Thr Ser Met Ser Pro Ser Ala Ala
 20 25 30
 Leu Ser Thr Gly Lys Pro Met Asp Ser His Pro Ser Tyr Thr Asp Thr
 35 40 45
 Pro Val Ser Ala Pro Arg Thr Leu Ser Ala Val Gly Thr Pro Leu Asn
 50 55 60
 Ala Leu Gly Ser Pro Tyr Arg Val Ile Thr Ser Ala Met Gly Pro Pro
 65 70 75 80
 Ser Gly Ala Leu Ala Ala Pro Pro Gly Ile Asn Leu Val Ala Pro Pro
 85 90 95
 Ser Ser Gln Leu Asn Val Val Asn Ser Val Ser Ser Ser Glu Asp Ile
 100 105 110
 Lys Pro Leu Pro Gly Leu Pro Gly Ile Gly Asn Met Asn Tyr Pro Ser
 115 120 125
 Thr Ser Pro Gly Ser Leu Val Lys His Ile Cys Ala Ile Cys Gly Asp
 130 135 140
 Arg Ser Ser Gly Lys His Tyr Gly Val Tyr Ser Cys Glu Gly Cys Lys
 145 150 155 160
 Gly Phe Phe Lys Arg Thr Ile Arg Lys Asp Leu Ile Tyr Thr Cys Arg
 165 170 175
 Asp Asn Lys Asp Cys Leu Ile Asp Lys Arg Gln Arg Asn Arg Cys Gln
 180 185 190
 Tyr Cys Arg Tyr Gln Lys Cys Leu Val Met Gly Met Lys Arg Glu Ala
 195 200 205
 Val Gln Glu Glu Arg Gln Arg Ser Arg Glu Arg Ala Glu Ser Glu Ala
 210 215 220
 Glu Cys Ala Thr Ser Gly His Glu Asp Met Pro Val Glu Arg Ile Leu
 225 230 235 240
 Glu Ala Glu Leu Ala Val Glu Pro Lys Thr Glu Ser Tyr Gly Asp Met
 245 250 255
 Asn Met Glu Asn Ser Thr Asn Asp Pro Val Thr Asn Ile Cys His Ala
 260 265 270
 Ala Asp Lys Gln Leu Phe Thr Leu Val Glu Trp Ala Lys Arg Ile Pro
 275 280 285
 His Phe Ser Asp Leu Thr Leu Glu Asp Gln Val Ile Leu Leu Arg Ala
 290 295 300
 Gly Trp Asn Glu Leu Leu Ile Ala Ser Phe Ser His Arg Ser Val Ser
 305 310 315 320
 Val Gln Asp Gly Ile Leu Leu Ala Thr Gly Leu His Val His Arg Ser
 325 330 335
 Ser Ala His Ser Ala Gly Val Gly Ser Ile Phe Asp Arg Val Leu Thr
 340 345 350
 Glu Leu Val Ser Lys Met Lys Asp Met Gln Met Asp Lys Ser Glu Leu
 355 360 365
 Gly Cys Leu Arg Ala Ile Val Leu Phe Asn Pro Asp Ala Lys Gly Leu
 370 375 380
 Ser Asn Pro Ser Glu Val Glu Thr Leu Arg Glu Lys Val Tyr Ala Thr
 385 390 395 400
 Leu Glu Ala Tyr Thr Lys Gln Lys Tyr Pro Glu Gln Pro Gly Arg Phe
 405 410 415
 Ala Lys Leu Leu Leu Arg Leu Pro Ala Leu Arg Ser Ile Gly Leu Lys

-27-

		420						425					430			
Cys	Leu	Glu	His	Leu	Phe	Phe	Phe	Lys	Leu	Ile	Gly	Asp	Thr	Pro	Ile	
		435						440				445				
Asp	Thr	Phe	Leu	Met	Glu	Met	Leu	Glu	Thr	Pro	Leu	Gln	Ile	Thr		
	450					455					460					

<210> 17
 <211> 1330
 <212> DNA
 <213> Homo Sapien

<220>
 <221> CDS
 <222> (97)...(837)

<300>
 <308> GeneBank XM_042579
 <309> 2002-02-06

<400> 17
 ttgggggttgt gctccagggga tggccttttca catagactgc agtgtaaagt acagcctctg 60
 gaatgtgcat tgcagggcct tgcttagtgg tagggga atg att tcc atc act tct 114
 Met Ile Ser Ile Thr Ser
 1 5

gtg aca ttc tgc ttc cca ata agt ctt cct gtg act tcc cta ttt ccc 162
 Val Thr Phe Cys Phe Pro Ile Ser Leu Pro Val Thr Ser Leu Phe Pro
 10 15 20

cca tcc cag att aac tca aca gtg tca ctc cct ggg ggt ggg tct ggc 210
 Pro Ser Gln Ile Asn Ser Thr Val Ser Leu Pro Gly Gly Gly Ser Gly
 25 30 35

ccc cct gaa gat gtg aag cca cca gtc tta ggg gtc cgg ggc ctg cac 258
 Pro Pro Glu Asp Val Lys Pro Pro Val Leu Gly Val Arg Gly Leu His
 40 45 50

tgt cca ccc cct cca ggt ggc cct ggg gct ggc aaa cgg cta tgt gca 306
 Cys Pro Pro Pro Pro Gly Gly Pro Gly Ala Gly Lys Arg Leu Cys Ala
 55 60 65 70

atc tgc ggg gac aga agc tca ggc aaa cac tac ggg gtt tac agc tgt 354
 Ile Cys Gly Asp Arg Ser Ser Gly Lys His Tyr Gly Val Tyr Ser Cys
 75 80 85

gag ggt tgc aag ggc ttc ttc aaa cgc acc atc cgc aaa gac ctt aca 402
 Glu Gly Cys Lys Gly Phe Phe Lys Arg Thr Ile Arg Lys Asp Leu Thr
 90 95 100

tac tct tgc cgg gac aac aaa gac tgc aca gtg gac aag cgc cag cgg 450
 Tyr Ser Cys Arg Asp Asn Lys Asp Cys Thr Val Asp Lys Arg Gln Arg
 105 110 115

aac cgc tgt cag tac tgc cgc tat cag aag tgc ctg gcc act ggc atg 498
 Asn Arg Cys Gln Tyr Cys Arg Tyr Gln Lys Cys Leu Ala Thr Gly Met
 120 125 130

aag agg gag gcg gta cag gag gag cgt cag cgg gga aag gac aag gat 546
 Lys Arg Glu Ala Val Gln Glu Glu Arg Gln Arg Gly Lys Asp Lys Asp
 135 140 145 150

ggg gat ggg gag ggg gct ggg gga gcc ccc gag gag atg cct gtg gac 594
 Gly Asp Gly Glu Gly Ala Gly Gly Ala Pro Glu Glu Met Pro Val Asp
 155 160 165

agg atc ctg gag gca gag ctt gct gtg gaa cag aag agt gac cag ggc 642

-28-

Arg Ile Leu Glu Ala Glu Leu Ala Val Glu Gln Lys Ser Asp Gln Gly
 170 175 180

gtt gag ggt cct ggg gga acc ggg ggt agc ggc agc agc gtg agt gtt 690
 Val Glu Gly Pro Gly Gly Thr Gly Gly Ser Gly Ser Ser Val Ser Val
 185 190 195

ggg gtc aat cca ctc tcc ttc gtg atg ggg gtt ggg gga ggc agt cta 738
 Gly Val Asn Pro Leu Ser Phe Val Met Gly Val Gly Gly Gly Ser Leu
 200 205 210

ggg ctg ttc tac atc ccc tcc ccc tcc ttt ccc ctc ata acc ttc cta 786
 Gly Leu Phe Tyr Ile Pro Ser Pro Ser Phe Pro Leu Ile Thr Phe Leu
 215 220 225 230

aca cta ctt ggg act gga ggt gct gcc aaa caa ggt ctt tca aac atc 834
 Thr Leu Leu Gly Thr Gly Gly Ala Ala Lys Gln Gly Leu Ser Asn Ile
 235 240 245

tga ggtggatgtg atagctcctt ctgtctccac tccccaaaca acccactggc 887
 *

agaaccatag gcatgtccca aataaataat tgtttgact aatgccagaa gagaagactc 947
 acttacaggg attgggtttgg atgggggctca caggaagact atatgtaagg aggggggtgtc 1007
 aaaagcctct tacaagggggg ctcccagcat atctcaaaat cttccataac tcttaccccc 1067
 gtcccttgca gccaaatgac cctgtgacta acatctgtca ggcagctgac aaacagctat 1127
 tcacgcttgt tgagtgggcg aagaggatcc cacacttttc ctccttgccct ctggatgatc 1187
 aggtcatatt gctgcgggca ggtcagtgac cttggatccc tttgacttct tgacatttga 1247
 cccctctttg acttcccgat ctttagtgac cccagtggcc ttaccttgcg taccagggga 1307
 gccaaacttg ctgacctgcg cac 1330

<210> 18
 <211> 246
 <212> PRT
 <213> Homo Sapien

<400> 18
 Met Ile Ser Ile Thr Ser Val Thr Phe Cys Phe Pro Ile Ser Leu Pro
 1 5 10 15
 Val Thr Ser Leu Phe Pro Pro Ser Gln Ile Asn Ser Thr Val Ser Leu
 20 25 30
 Pro Gly Gly Gly Ser Gly Pro Pro Glu Asp Val Lys Pro Val Leu
 35 40 45
 Gly Val Arg Gly Leu His Cys Pro Pro Pro Gly Gly Pro Gly Ala
 50 55 60
 Gly Lys Arg Leu Cys Ala Ile Cys Gly Asp Arg Ser Ser Gly Lys His
 65 70 75 80
 Tyr Gly Val Tyr Ser Cys Glu Gly Cys Lys Gly Phe Phe Lys Arg Thr
 85 90 95
 Ile Arg Lys Asp Leu Thr Tyr Ser Cys Arg Asp Asn Lys Asp Cys Thr
 100 105 110
 Val Asp Lys Arg Gln Arg Asn Arg Cys Gln Tyr Cys Arg Tyr Gln Lys
 115 120 125
 Cys Leu Ala Thr Gly Met Lys Arg Glu Ala Val Gln Glu Glu Arg Gln
 130 135 140
 Arg Gly Lys Asp Lys Asp Gly Asp Gly Glu Gly Ala Gly Gly Ala Pro
 145 150 155 160
 Glu Glu Met Pro Val Asp Arg Ile Leu Glu Ala Glu Leu Ala Val Glu
 165 170 175
 Gln Lys Ser Asp Gln Gly Val Glu Gly Pro Gly Gly Thr Gly Gly Ser
 180 185 190
 Gly Ser Ser Val Ser Val Gly Val Asn Pro Leu Ser Phe Val Met Gly
 195 200 205
 Val Gly Gly Gly Ser Leu Gly Leu Phe Tyr Ile Pro Ser Pro Ser Phe
 210 215 220
 Pro Leu Ile Thr Phe Leu Thr Leu Leu Gly Thr Gly Gly Ala Ala Lys

-29-

225
Gln Gly Leu Ser Asn Ile
245

235

240

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US02/41306

A. CLASSIFICATION OF SUBJECT MATTER

IPC(7) : C07D 213/64; A61K 31/4412, 31/4418

US CL : 546/268.1, 290, 302; 514/336, 345

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 546/268.1, 290, 302; 514/336, 345

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

CAS Online: CAPLUS, REGISTRY, structure search; EAST, WEST

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	Database CAPLUS on ACS, AN 1987: 458776, GUTCAIT, A., et al. Synthesis, structure, and properties of 1-amino-6-phenyl-4-trifluoromethyl-3-cyano-2-pyridone. Latvijas PSR Zinatnu Akademijas Vestis, Kimijas Serija. 1986, Vol. 5, pages 607-12.	2, 3
X	Database CAPLUS on ACS, AN 1988:167259, JURE, M. et al. 1-Methyl-6-phenyl-4-trifluoromethyl-3-cyano-2-pyridone and its properties. Latvijas PSR Zinatnu Akademijas Vestis, Kimijas Serija. 1987, Vol. 5, pages 627-31.	2, 3

☐ Further documents are listed in the continuation of Box C.

☐ See patent family annex.

* Special categories of cited documents:	
"A" document defining the general state of the art which is not considered to be of particular relevance	"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"E" earlier application or patent published on or after the international filing date	"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"O" document referring to an oral disclosure, use, exhibition or other means	"&" document member of the same patent family
"P" document published prior to the international filing date but later than the priority date claimed	

Date of the actual completion of the international search

30 April 2003 (30.04.2003)

Date of mailing of the international search report

05 JUN 2003

Name and mailing address of the ISA/US

Mail Stop PCT, Attn: ISA/US
Commissioner for Patents
P.O. Box 1450
Alexandria, Virginia 22313-1450

Facsimile No. (703)305-3230

Authorized officer

Telicia D. Roberts for
Alan Rotman

Telephone No. 703.308.1235

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US02/41306

Box I Observations where certain claims were found unsearchable (Continuation of Item 1 of first sheet)

This international report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claim Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
2. ☒ Claim Nos.: 1 and 126-140
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
Please See Continuation Sheet
3. ☒ Claim Nos.: 4-125
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of Item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐
☐

The additional search fees were accompanied by the applicant's protest.

No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US02/41306

Continuation of Box I Reason 2:

In these claims, the numerous variables (e.g. n, q, r, x, y, z, R1, R2, R3, R4, R5, R6, R7, R8, R9, R10, R30, R31, R32, R35, R40, X, J, Q1, Q2, etc), their voluminous complex meanings, their seemingly endless permutations and combinations and the numerous provisos make it virtually impossible to determine the full scope and complete meaning of the claimed subject matter. As presented, the claimed subject matter cannot be regarded as being a clear and concise description for which protection is sought and as such the listed claims do not comply with the requirements of PCT article 6. Thus it is impossible to carry out a meaningful search on same. A search will be made on the first discernable invention of claim 2, which is example 2, compound 2, found on page 150 of the specification.